Syllabus

AUA 60th Annual Meeting

April 4-6, 2013

JW Marriott Marquis • Miami, Florida

This activity has been approved for

AMA PRA Category 1 Credits™.

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AUA
Association of University Anesthesiologists
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Welcome to the AUA 60th Annual Meeting in Miami, Florida!

The Department of Anesthesiology at the University of Miami's Miller School of Medicine is proud to host the 60th Annual Meeting of the Association of University Anesthesiologists. We wish to extend to the AUA membership a warm welcome to Miami – one of the trendiest coastal cities within the U.S. Our mixtures of clubs, restaurants and stores *(along with a thriving visual and performing arts district)* have become one of the biggest tourist destinations in the country! We also offer some of the finest weather around, unbeatable beaches, and we are pleased that you are here with us.

It is important to note that our medical school's history is intertwined with that of the AUA through the legacy of the renowned Dr. Emanuel M. Papper, a co-founder of the AUA and a pioneer in our field. In 1969, Dr. Papper was recruited from Columbia and became Dean of the University of Miami School of Medicine. During his tenure, the school made important strides in research, education, and patient care. Under his leadership, research funding for the school increased by 70 percent - placing it 20th among the nation's 119 medical schools. Dr. Papper also guided the institution during the establishment of the Public Health Trust, a public body which helped to arrange for funding of indigent care and the establishment of Miami's only Level 1 Trauma center. Unmistakably, Dean Papper's vision for the medical school continues to be fulfilled under the current guidance of Dean Goldschmidt, as the institution has re-emerged as both a top tier research enterprise and expanding clinical powerhouse in the region. This undeniably also reflects on the fine leadership of our President, Donna E. Shalala.

We have a tremendous array of lectures and social events arranged during the course of the meeting. I encourage all present to spend a few minutes and visit the special exhibit that will be on display which pays tribute to Dr. Papper and his career as teacher, clinician, researcher, colleague and friend.

Special recognition must be afforded to Dr. Michael C. Lewis, a faculty member in my department who also serves as the Senior Associate Dean for Graduate Medical Education. The attention to detail and the exciting program to follow is typical of all of Michael's professional undertakings. Dr. Lewis, along with AUA leadership and administrative support personnel, deserve our gratitude.

Sincerely,

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Program Objectives

EAB Part 1: Performance Measurement - Does it Matter?

At the conclusion of the session, the attendee should be able to:

- Have a basic understanding of performance measures in anesthesia practice, describe the benefits that can be obtained, and outline the potential risks.

EAB Part 2: Faculty Development

At the conclusion of the session, the attendee should be able to:

- Identify risk factors for faculty attrition.
- Understand what is "burnout" and devise a plan for its prevention.

SAB Plenary Lecture

At the conclusion of the session, the attendee should be able to:

- Recognize how novel anesthetic receptors play a key role in health and disease.
- Explain how anesthetic actions at the molecular level can guide clinical practice.

SAB Oral Sessions

At the conclusion of the session, the attendee should be able to:

- Recognize a broad range of current basic science and clinical research in anesthesiology and critical care medicine.

SAB Research Funding Session

Anesthesiology Foundation Funding Opportunities

At the conclusion of the session, the attendee should be able to:

- Identify a range of research interests supported by funding opportunities from anesthesiology foundations.

Program Information

Target Audience

This meeting is designed for anesthesiologists in the clinical and laboratory setting who desire to improve development of anesthesiology teaching methods by engaging in an interchange of ideas as represented in this meeting.

Needs Assessment

Topics for this meeting were derived from evaluations from the 2012 and previous annual meetings. Suggested topics were discussed and developed by educators who attended previous Annual, Council and Advisory Board meetings and by other authorities in the field of anesthesia education.

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Miami Miller School of Medicine and the Association of University Anesthesiologists. The University of Miami Miller School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

The University of Miami Leonard M. Miller School of Medicine designates this live activity for a maximum of 13.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Faculty Disclosure

All conflicts of interest of any individuals in a position to control the content of this CME activity will be identified and resolved prior to this educational activity being provided. Disclosure about provider and faculty relationships, or the lack thereof, will be provided to the learners.

Special Needs Statement

The University of Miami Health System and the Association of University Anesthesiologists are committed to making its activities accessible to all individuals. If you are in need of a special accommodation, please do not hesitate to call the AUA office at (847) 825-5586 and/or submit a description of your needs in writing to c.dionne@asahq.org at least two weeks prior to the meeting.

Disclaimer

The information in this educational activity is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient's medical condition. The viewpoints expressed in this CME activity are those of the authors/faculty. They do not represent an endorsement by the University of Miami Miller School of Medicine. In no event will the University of Miami Miller School of Medicine be liable for any decision made or action taken in reliance upon the information provided through this CME activity.

General Information

Identification Badges
Participants will receive a name badge, which will serve as admission to all scientific sessions, lunches and social events. Your badge must be worn at all times in order to enter all AUA 60th Annual Meeting functions.

Cell Phones and Beepers
Cell phones and beepers should be turned off or on vibrate. We thank you for your cooperation.

Phone Messages
The phone number for the JW Marriott Marquis is (305) 421-8600. Please ask callers to request the AUA 60th Annual Meeting Registration Desk by its full name. All messages will be posted on the message board near the Registration Area. Messages will not be announced, so please check the message board frequently if you anticipate messages.

Attendee Interaction
Attendee participation is strongly encouraged. Standing microphones will be placed in each aisle to facilitate question and answer sessions. Those attendees asking questions are encouraged to use the microphones.

Meeting Evaluations and Continuing Medical Education Certificates
The University of Miami Miller School of Medicine requires that each attendee complete and return the meeting evaluation form as well as the Physicians Verification of Attendance form (both located in the meeting folder).

Resident and Junior Faculty Meet and Greet Reception
Thursday, April 4, 2013, 5:30 – 6:00 p.m.
Plaza Room 1 (5th Floor)
(Included in the Resident/Fellow registration fee)
A return feature from last year is the Resident and Junior Faculty Meet and Greet Reception. This reception gives residents, fellows, and junior faculty an opportunity to meet their peers, the FAER Academy of Research Mentors and AUA Council members in an informal setting before the start of the formal program.

Welcome Reception
Thursday, April 4, 2013, 6:00 – 8:00 p.m.
Pool Deck (19th Floor)
AUA meeting attendees are encouraged to attend the Welcome Reception. This is an ideal opportunity to catch up with friends and colleagues.

Evening Social Event
Saturday, April 6, 2013, 6:00 – 10:00 p.m.
J.W. Marriott Marquis (19th Floor)
Join your friends and colleagues for a perfect ending to the 60th Annual Meeting. This Saturday event offers an opportunity to unwind, relax, and enjoy live music by Atlas Shrugged.

Poster Presentations
Poster viewing is scheduled for each coffee break. The Scientific Advisory Board (SAB) will moderate the poster sessions. The following are members of the Scientific Advisory Board:

Dean B. Andropoulos, M.D.
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Houston, Texas

Charles Emala, Sr., M.D.
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New York, New York

Pamela Flood, M.D.
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Disclosures

Faculty and Program Committee Disclosures

The following individuals (faculty and/or program committee members) have disclosed that they have no relevant financial relationships with any commercial interests related to the content of this educational activity.

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Denham Ward, M.D.
John M. Zerwas, M.D.

Oral and Poster Presentation Disclosures

Each Oral and Poster Presenter is required to disclose the existence of any financial interest and/or other relationship(s) (e.g. employee, consultant, grant recipient/research support he/she might have with a) the manufacturer(s) of any commercial product(s) to be discussed during his/her presentation and/or b) the commercial contributor(s) of the activity.

1= Ownership
2= Grants/Research Support
3= Funded Research
4= Consultant
5= Equity Position
6= Royalties
7= Honoraria
8= Teaching and Speaking

The following individuals (Oral and Poster Presenters) have reported the listed relevant financial relationships with commercial interests related to the content of this educational activity.

Fred S. Apple, Ph.D.	3 - Abbott, Ortho-Clinical Diagnostics, Siemens, Roche Diagnostics, Radiometer
E. Wesley Ely, M.D.	7 - Hospira, Eli Lily, Abbott
Christopher Fraker, Ph.D.	5 - NEVA scientific
Kyota Fukazawa, M.D.	5 - NEVA scientific
Timothy D. Girard, M.D.	7 - Hospira
Allan S. Jaffe, M.D.	4 - Beckman, Ortho, Abbott, Alere, Critical Diagnostics, Roche, Amgen, the Heart.org
Jonathan Moss, M.D., Ph.D.	6, 4 - Salix Pharmaceuticals
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All conflicts of interest have been resolved.

Program Schedule

Thursday, April 4, 2013

10:00 a.m. - 6:00 p.m.	**Registration**	3rd Floor Atrium
1:00 - 1:15 p.m.	**Introduction and Welcome to the 60th Annual Meeting** David A. Lubarsky, M.D., M.B.A.	Met 1
1:15 - 1:30 p.m.	**SAB Program Introduction** Charles W. Emala, M.D.	Met 1
1:30 - 3:00 p.m.	**SAB Oral Session (Part 1)**	Met 1
	Junior Faculty Presentation	
Junior Faculty Award	**A Novel Strategy to Treat Human Pre-Term Labor - Targeting the TMEM16/Anoctamin Chloride Channel in Human Pregnant Uterus** George Gallos, M.D.	
	Resident Presentation	
Resident Travel Award	**Stimulation of Stimulation of Î±2-Adrenergic Receptors Antagonizes Isoflurane-Induced Activation of Sleep-promoting VLPO Neurons and Partially Attenuates Anesthetic Hypnosis** Michael R. Chalifoux, M.D.	
	Oral Presentations	
	Isoflurane Overcomes Defective Programmed Cell Death in the Developing Brain of Autistic Mice Richard J. Levy, M.D.	
	In Vivo Application of Engineered Receptors for Treatment of Acute and Chronic Pain Yan Xu, Ph.D.	
	Hypobaric Oxygenation During Cardiopulmonary Bypass Eliminates Gaseous Microemboli and Reduces Microvascular Injury in Swine Keith E. Gipson, M.D., Ph.D.	
	Cognitive Dysfunction and Early Mortality Following Carotid Endarterectomy Eric J. Heyer, M.D., Ph.D.	
	CW 1759-50 An Ultra-Short Acting Nondepolarizer Immediately Antagonized at Any Time by L-Cysteine John J. Savarese, M.D.	
	NOVA1 Variants Regulate RNA Splicing at The Inhibitory Synapse and Persistent Pain Susceptibility Roy C. Levitt, M.D.	
3:00 - 4:30 p.m.	**Moderated Poster Discussion Session** Moderator: Charles W. Emala, M.D.	Met 5, 6, 7
5:30 - 6:00 p.m.	**Resident and Junior Faculty Meet and Greet Reception**	Plaza Room 1
6:00 - 8:00 p.m.	**Welcome Reception**	Pool Deck, 19th Floor

Program Schedule

Friday, April 5, 2013

6:30 a.m. - 5:30 p.m.	**Registration**	3rd Floor Atrium
7:00 a.m. - 8:00 a.m.	**Continental Breakfast**	Metropolitan Prefunction South
8:15 - 9:45 a.m.	**EAB Program (Part 1) Performance Measurement: Does It Matter?** Moderator: Richard P. Dutton, M.D., M.B.A. **Pro:** Lee A. Fleisher, M.D. **Con:** Avery Tung, M.D., FCCM	Met 1
9:45 - 10:15 a.m.	**Poster Viewing and Discussion** Moderator: Charles W. Emala, M.D.	Met 5, 6, 7
10:15 - 11:45 a.m.	**EAB Program (Part 2) Faculty Development** Moderator: T.J. Gan, M.D. • **Challenges and Solutions to Mentorship in Anesthesiology** Monica S. Vavilala, M.D. • **Faculty Attrition: Is it a Problem?** Brenda A. Bucklin, M.D. • **Burnout or Whining, You Decide** Robert R. Gaiser, M.D.	Met 1
11:45 a.m. - 1:00 p.m.	**Luncheon**	Met 2, 3, 4
11:45 a.m. - 1:00 p.m.	**EAB Luncheon**	Plaza Room 1
	SAB Luncheon	Plaza Room 2
	Presidents' Luncheon	Plaza Room 3
1:00 - 1:30 p.m.	**ASA President's Update** Jerry Cohen, M.D.	Met 1
1:30 - 2:30 p.m.	**SAB Plenary Lecture** **Anesthetics - The Final Frontier** Beverley A. Orser, M.D., Ph.D.	Met 1
2:30 - 3:00 p.m.	**Break/Poster Viewing**	Met 5, 6, 7
3:00 - 4:30 p.m.	**Anesthesiology Foundation Funding Opportunities**	Met 1
3:00 - 3:20 p.m.	**FAER Funding** Denham Ward, M.D., Ph.D.	
3:20 - 3:40 p.m.	**IARS Funding** Alex S. Evers, M.D.	
3:40 - 4:05 p.m.	**SCA Funding** Joyce A. Wahr, M.D.	
4:05 - 4:30 p.m.	**APSF Funding** Steven K. Howard, M.D.	
4:30 - 5:30 p.m.	**AUA Business Meeting**	Met 1

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Program Schedule

Saturday, April 6, 2013

6:30 a.m. – 5:00 p.m.	**Registration**	3rd Floor Atrium
7:00 – 8:00 a.m.	**Continental Breakfast**	Metropolitan Prefunction South
8:00 a.m. - Noon	**Host Program** Michael C. Lewis, M.D. *CME is not provided for this portion of the program* **Where We Live?** • **Our Climate:** Roni Avissar, Ph.D. • **Our Buildings:** Elizabeth Plater-Zyberk • **Our Neighbors:** Andy S. Gomez, Ph.D. **What We Do?** • **Physics of Collective Behavior:** Neal Johnson, M.D. • **Aging and Spirituality:** Stephen Sapp, Ph.D. • **Genomics of Alzheimer's:** Margaret A. Pericak-Vance, Ph.D.	Met 1
10:00 – 10:30 a.m.	**Break/Poster Viewing and Discussion**	Met 5, 6, 7
Noon. - 1:30 p.m.	**All Attendee Luncheon (Residents at Reserved tables)**	Met 2, 3, 4
1:30 – 1:40 p.m.	**SAB Program Introduction** Charles W. Emala, M.D.	Met 1
1:30 - 3:00 p.m.	**SAB Oral Session (Part 2)**	Met 1
	Junior Faculty Presentation	
Junior Faculty Award	**Optogenetic Stimulation of Dopamine Neurons in the Ventral Tegmental Area** Norman E. Taylor, M.D., Ph.D.	
	Resident Presentation	
Resident Travel Award	**Novel Chloride Channel Blockers Relax Airway Smooth Muscle: Potential New Tools to Treat Bronchospasm** Jennifer Danielsson, M.D.	
	Oral Presentations	
	General Anesthesia Causes Disturbances of Mitochondrial Morphogenesis and Synaptic Transmission in Developing Rat Brain Nadia Lunardi, M.D, Ph.D.	
	Modeling the Ischemic Penumbra in C. Elegans C. Michael Crowder, M.D., Ph.D.	
	Zero Tolerance for Chronic Pain Howard B. Gutstein, M.D.	
	Critical Role of Interleukin-11 in Isoflurane-Mediated Protection Against Ischemic Acute Kidney Injury H.T. Lee, M.D., Ph.D.	
	MicroRNAs and Anesthetic Cardioprotection in Diabetes Zeljko J. Bosnjak, Ph.D.	
	Percutaneous Fiber Optic Monitoring for Spinal Cord Ischemia Angela D'Souza, M.S., BME	
3:00 – 5:00 p.m.	**Poster Viewing and Discussion** Moderator: Charles W. Emala, M.D.	Met 5, 6, 7
6:00 - 10:00 p.m.	**Social Event – JW Marriott Marquis Miami** **6:00 - 7:00 p.m. Reception** **7:00 - 10:00 p.m. Dinner and Music**	19th Floor

Program Material

Thursday, April 4, 2013

SAB Oral Session (Part 1)

Junior Faculty Presentation (Junior Faculty Award)

A Novel Strategy to Treat Human Pre-Term Labor - Targeting the TMEM16/Anoctamin Chloride Channel in Human Pregnant Uterus
George Gallos, M.D.; Herng-Yu Sucie Chang, Ph.D.; Wen Fu, Ph.D.; Elizabeth Townsend, Ph.D.; Hiromi Funayama, D.D.S., Ph.D.; Charles W. Emala, M.D.

Resident Presentation (Resident Travel Award)

Stimulation of Î±2-Adrenergic Receptors Antagonizes Isoflurane-Induced Activation of Sleep-promoting VLPO Neurons and Partially Attenuates Anesthetic Hypnosis
Michael R. Chalifoux, M.D.; Hilary McCarren, B.S.; Bo Han, M.D., Ph.D.; Matthew Fleisher; Sheryl Beck, Ph.D.; Max Kelz, M.D., Ph.D.

Oral Presentations

Isoflurane Overcomes Defective Programmed Cell Death in the Developing Brain of Autistic Mice
Richard J. Levy, M.D.; Ying Cheng, B.S.

In Vivo Application of Engineered Receptors for Treatment of Acute and Chronic Pain
Yan Xu, Ph.D.; Yoshika Takahashi, M.D.; Tommy S. Tillman, Ph.D.; Nicole R. Brandon, M.S.; Pei Tang, Ph.D.

Hypobaric Oxygenation During Cardiopulmonary Bypass Eliminates Gaseous Microemboli and Reduces Microvascular Injury in Swine
Keith E. Gipson, M.D., Ph.D.[1]; Robert B. Schonberger, M.D., M.A.[2]; Jeffrey B. Gross, M.D.[1]

Cognitive Dysfunction and Early Mortality Following Carotid Endarterectomy
Eric J. Heyer, M.D., Ph.D.; Joanna L. Mergeche, B.A.; Joanne Brady, M.S.; Charles J. DiMaggio, Ph.D.; Samuel S. Bruce, M.S.; E. Sander Connolly, M.D.

CW 1759-50 An Ultra-Short Acting Nondepolarizer Immediately Antagonized at Any Time by L-Cysteine
John J. Savarese, M.D.[1]; Hiroshi Sunaga, M.D.[1]; Matthew R. Belmont, M.D.[1]; Matthew Murrell, M.D., Ph.D.[1]; Paul M. Heerdt, M.D., Ph.D.[1]; Jeff McGilvra, Ph.D.[2]

NOVA1 Variants Regulate RNA Splicing at The Inhibitory Synapse and Persistent Pain Susceptibility
Roy C. Levitt, M.D.[1]; Yan Ping Zhang, M.D.[1]; Shad Smith, Ph.D.[2]; William Maixner, DDO, Ph.D.[2]; Luda Diatchenko, M.D., Ph.D.[2]; Jian Guo Cui, M.D., Ph.D.[1]; Diana Erasso, Ph.D.[1]; Zhiye Zhuang, Ph.D.[1]; Eden Martin, Ph.D.[1]; Susan Slifer, MS[1]; Eugene S. Fu, M.D.

Junior Faculty Award

A Novel Strategy to Treat Human Pre-Term Labor - Targeting the TMEM16/Anoctamin Chloride Channel in Human Pregnant Uterus

George Gallos, M.D.; Herng-Yu Sucie Chang, Ph.D.; Wen Fu, Ph.D.; Elizabeth Townsend, Ph.D.; Hiromi Funayama, D.D.S., Ph.D.; Charles W. Emala, M.D.
Columbia University

Introduction: Pre-term labor is a major health challenge that is associated with high maternal and fetal morbidity. Since the pharmacologic armamentarium for treating pre-term labor has limited efficacy, novel mechanisms capable of promoting uterine smooth muscle tocolysis are clinically valuable to suppress pre-term labor. We have previously described the expression of mRNA from the TMEM16/Anoctamin family of calcium activated chloride channels in murine as well as human myometrium and showed that TMEM16A antagonists suppress stretch-induced uterine contractions in a murine model. In the current group of studies, we questioned the functional implications of TMEM16A blockade on in vitro pregnant human uterine smooth muscle contractions generated by exogenous oxytocin. We also examined the ability of TMEM16A antagonists to: 1) suppress spontaneous transient inward chloride currents (STICs) (electrophysiologic phenomena associated with rhythmic contractile waves) by whole cell electrophysiology and 2) abolish oxytocin-induced elevations of intracellular calcium using real-time fluorescence imaging.

Methods: Following IRB approval, samples of pregnant human myometrium were obtained during C-section and processed for either in vitro contractile studies or were primarily dissociated to establish primary uterine smooth muscle cell cultures. To assess the functional implications of TMEM16A blockade on pregnant human uterine smooth muscle contractions, we performed organ bath experiments on excised uterine segments examining the effect of a TMEM16A inhibitor, tannic acid (200uM) on subsequent oxytocin-induced (1uM) contraction frequency and force (integrated over a period of 25 minutes). Primary human uterine smooth muscle cells were loaded with the calcium indicator Fluo-4 and the ability of tannic acid (100uM) to inhibit subsequent oxytocin-induced (1uM) calcium release was assessed with confocal microscopy. Data is presented as mean ± SEM; $p < 0.05$ was considered significant.

Results: Treatment with the TMEM16A antagonist tannic acid attenuated both the frequency (4.6± 1.3 contractions/25 min; n=5; Figure 1B) and integrated force (8446±1250 gm*sec/25 min; n=5; Figure 1C) of oxytocin-induced human uterine contractions when compared to the frequency and force measured in vehicle controls (17.4±1.4 contractions/25min; n=6; p=0.0001 and 18814±3010 gm*sec/25 min; n=4; p=0.01 respectively). Pretreatment with the TMEM16A antagonist (tannic acid 100uM) also attenuated oxytocin-(1uM) induced calcium release (5.45±2.30 ΔRFU; n=8) compared to vehicle controls (212.2±53.15 ΔRFU; n=5; p=0.01). Additionally, TMEM16A blockade reduced oxytocin-enhanced uterine smooth muscle cell pro-contractile electrophysiologic current amplitude (0.28±0.10 pA; n=4 vs 2.09±0.57 pA; n=4; p=0.020) and frequency (0.21±0.09 Hz; n=4 vs. 4.10±1.3 Hz; n=4; p= 0.025).

Conclusion: TMEM16A is expressed in human pregnant uterine smooth muscle cells. Blockade of TMEM16A attenuates oxytocin-induced contractions, abolishes oxytocin-induced calcium release and suppresses human uterine electrical STIC activity. Targeted blockade of endogenous TMEM16 receptors may represent a novel therapeutic option for patients in pre-term labor.

Resident Travel Award

Stimulation of Î±2-Adrenergic Receptors Antagonizes Isoflurane-Induced Activation of Sleep-promoting VLPO Neurons and Partially Attenuates Anesthetic Hypnosis

Michael R. Chalifoux, M.D.; Hilary McCarren, B.S.; Bo Han, M.D., Ph.D.; Matthew Fleisher; Sheryl Beck, Ph.D.; Max Kelz, M.D., Ph.D.
University of Pennsylvania

The ventrolateral preoptic (VLPO) nucleus of the hypothalamus plays a significant role in both sleep and anesthetic-induced hypnosis.[1] We have previously shown that the volatile agent, isoflurane (ISO), directly depolarizes sleep-promoting VLPO neurons while not affecting neighboring non-sleep-promoting VLPO neurons.[2] However, in the acute setting, the behavioral significance of sleep-promoting VLPO activation remains unknown.[2,3] If anesthetic-induced depolarization of sleep-promoting neurons were essential to hypnosis, then hyperpolarizing these neurons should attenuate the hypnotic state. We hypothesize that local pharmacologic treatment of sleep-promoting VLPO with dexmedetomidine (DEX) will antagonize both isoflurane-induced depolarization as well as its behavioral hypnosis in intact animals.

Using hypothalamic slices prepared from wild type C57BL6J mice, whole-cell current clamp recordings were conducted. VLPO neurons were classified as putative sleep-promoting based upon a hyperpolarizing response to a bath application of 100µM norepinephrine (NE).[2,4,5] To determine the mechanism of adrenergic-induced hyperpolarization, the highly potent and specific 2A adrenergic agonist, DEX, was bath-applied. In 7/7 putative sleep-promoting VLPO neurons, 100nM DEX also caused a hyperpolarization (-43 ± 2.7mV resting membrane potential (RMP) to -50 ± 2.3mV DEX, p=0.0014). Sleep-promoting VLPO neurons exposed to 330µM ISO alone depolarized (-48.6 ± 2.1mV RMP to -39.9 ± 4.1mV ISO, p=0.0004) and increased firing rates (0.06 ± 0.09Hz baseline to 0.5 ± 0.44Hz ISO, p=0.0112) in 6/6 cells. Concomitant administration of 100nM DEX plus 330µM ISO hyperpolarized the membrane (-39.9 ± 4.1 mV RMP to -45.98 ± 4.32mV DEX+ISO, p=0.0004) and decreased the firing rates (0.5 ± 0.44Hz ISO to 0.04 ± 0.09Hz DEX+ISO, p=0.0112) of all 6 neurons; thus reversing ISO's effects.

In 3/3 non-sleep-promoting, NE depolarized VLPO neurons, DEX did not significantly alter membrane potential or firing. Multiplex RT-PCR performed on single-cell cytoplasmic aspirates harvested from sleep-promoting VLPO neurons upon completion of electrophysiologic recordings,[6] confirmed the presence of 2A, 2B, and 2C adrenoceptors in DEX-hyperpolarized neurons.

To determine the functional significance of DEX's actions in VLPO, indwelling bilateral cannulae were used to deliver 25nl of adrenergic ligands into VLPO of mice stably anesthetized at 0.8% ISO or 500µm more caudally. During the 10 minutes prior to and 5 minutes following drug infusion, arousal state behavioral scores ranging from 0 (no movement) to 4 (full return of righting reflex) were assigned.[7] DEX delivered to VLPO caused a significant increase in arousal, while no change was observed with saline or the 1 agonist phenylephrine infusion in the same animals ($p<0.05$). Mice with more caudally placed cannulae exhibited no change in arousal with any drug. Though DEX nanoinjections in VLPO were able to arouse lightly anesthetized animals, no effects were seen in animals exposed to 1% ISO. These results suggest a significant contribution of adrenergic receptor signaling in VLPO in modulating hypnosis and builds upon the shared neuronal framework for sleep neurobiology and anesthetic mechanisms.

Oral Presentations

Isoflurane Overcomes Defective Programmed Cell Death in the Developing Brain of Autistic Mice

Richard J. Levy, M.D.; Ying Cheng, B.S.
Children's National Medical Center

Introduction: Fragile X Syndrome (FXS) is the leading known genetic cause of autism. The syndrome, caused by a mutation in the Fmr1 gene, silences Fragile X mental retardation protein (FMRP) expression and results in aberrant synapses and excess number of neurons. Defects in programmed cell death (PCD) could impair neuron pruning and developmental apoptosis has been shown to be deficient in Fmr1 mutant drosophila. We hypothesize that PCD is impaired in the developing brain of Fmr1 mutant mice and that anesthetics can overcome such defects. In this work, we assessed the intrinsic apoptosis pathway in the developing brain of two different Fmr1 mutant mouse strains and aimed to determine if isoflurane could therapeutically enhance PCD in these mice.

Methods: The care of the animals in this study was in accordance with NIH and Institutional Animal Care and Use Committee guidelines. We evaluated 10 day old Fmr1 null and Fmr1I304N mutant male mice with appropriate FVB and C57Bl/6 controls on P10. Apoptosis was assessed via immunohistochemistry for activated caspase-3 and TUNEL assays and neuronal quantity determined with cresyl violet staining. Levels of cytochrome c, procaspase-9, APAF-1, Bax, BCL-2, and BCL-xL were measured with immunoblotting. Separate cohorts underwent 1-hour exposure to isoflurane (2%) in air versus air alone on P10. Immunohistochemistry for activated caspase-3 was performed 5 hours post exposure. N=5 per group. Significance was assessed with ANOVA.

Results: 10 day old Fmr1 knockout and Fmr1I304N male mice demonstrated decreased activated caspase-3 and TUNEL positive nuclei in neocortex, hippocampus, and basolateral amygdala and excess number of neurons in primary somatosensory neurocortex and CA3 region of the hippocampus compared to controls. Although both Fmr1 mutant strains demonstrated intact Bax translocation, mitochondrial release of cytochrome c and procaspase-9 was impaired and expression of the anti-apoptotic protein, BCL-xL was increased. Isoflurane exposure increased the number of activated caspase-3 positive cells in neocortex and hippocampus of all animals and restored PCD to control values in Fmr1 mutants.

Discussion: The developing brain of FXS mice demonstrated impaired PCD and excess neurons. Release of pro-apoptotic mediators from mitochondria was impaired in both Fmr1 mutants likely due to increased levels of the anti-apoptotic protein, BCL-xL. Isoflurane, known to decrease BCL-xL and increase cytochrome c release from mitochondria, enhanced apoptosis in the developing forebrain of Fmr1 mutant mice and restored PCD to normal levels. Thus, it is possible that anesthetic agents could overcome defects in PCD to therapeutically enhance neuron pruning and eliminate excess synaptic connections in order to normalize behavior in FXS and autism.

Oral Presentations

In Vivo Application of Engineered Receptors for Treatment of Acute and Chronic Pain

Yan Xu, Ph.D.; Yoshika Takahashi, M.D.; Tommy S. Tillman, Ph.D.; Nicole R. Brandon, M.S.; Pei Tang, Ph.D.
University of Pittsburgh School of Medicine

Acute and chronic pain affects more people than cancer, heart disease, and diabetes combined. Treatment options are limited and often involve continuous use of analgesics, which frequently leads to the development of drug tolerance, dependence or abuse. Here we present a new strategy of pain medication by the installation of non-naturally occurring, engineered chloride channel receptors in peripheral nerves so that these nerves can be conditionally hyperpolarized by small molecules that otherwise have no or negligible analgesic effects. The chloride selectivity of the engineered channels and their activation by otherwise non-analgesic primary amines were established by in vitro electrophysiology measurements in oocytes. In vivo expression of the engineered channels in the peripheral nerve endings and dorsal root ganglia in rats was successful and showed no measurable interference with nociception under normal physiological conditions. After the injection of complete Freund's adjuvant (CFA) to induce inflammation in the hind paw, behavioral pain testing showed insignificant differences in pain scores when the engineered channels were not activated. Upon activation, significant alleviation of CFA-induced hyperalgesia and allodynia was observed and quantified. These results demonstrate the clinical potential of a fundamentally different class of therapeutics that are devoid of any centrally acting psychoactive effects and can potentially revolutionize the management of acute and chronic pain. (Funded in part by grants from the NIH, R37GM049202, R01GM056257, and R01GM066358)

Oral Presentations

Hypobaric Oxygenation During Cardiopulmonary Bypass Eliminates Gaseous Microemboli and Reduces Microvascular Injury in Swine

Keith E. Gipson, M.D., Ph.D.[1]; Robert B. Schonberger, M.D., M.A.[2]; Jeffrey B. Gross, M.D.[1]
University of Connecticut[1]; Yale University[2]

Introduction: Successful cardiac surgeries are frequently complicated by cognitive deficits of multifactorial etiology that degrade quality of life and increase healthcare costs. Gaseous microemboli (GME) contribute to several possible etiologies, and they occur by the thousands during cardiopulmonary bypass (CPB). Vasooclusive GME cause tissue ischemia and damage endothelium, leading to vascular dilation and permeability, activation of platelets and clotting cascades, and recruitment of complement and cellular mediators of inflammation. We previously presented a novel approach to oxygenation that practically eliminates GME delivery from the CPB circuit. Here, we extend our mechanistic understanding of GME removal and assess the impact of hypobaric oxygenation on brain tissue in swine.

Methods: Hypobaric oxygenation was performed using a sealed hollow fiber microporous membrane oxygenator and 100% O2 sweep gas at variable subatmospheric pressures. The control condition used O2/air sweep gas at ambient pressure. Dissolved N2 was measured by mass spectrometry. GME were counted and sized using multisite Doppler detection in the CPB circuit: before and after the oxygenator, after the filter, and just before the patient. A veterinary pathologist examined formalin-fixed brain tissue in hematoxylin/eosin sections. A blinded observer measured dilated capillaries (SCAD) in 10x fields of white matter adjacent to the lateral ventricle. Data presented use mean ± SEM and Student's T-test.

Results: We hypothesized that subatmospheric sweep gas pressures would lower O2 partial pressures and achieve normoxic blood gas values while denitrogenating the blood and tissues of the patient, thereby accelerating reabsorption of air from GME into the aqueous phase. Indeed, hypobaric oxygenation denitrogenated blood by at least 85 +/- 1% from baseline (n=3, $P<0.001$). GME removal by the oxygenator, by the arterial filter, and in flowing blood were all substantially improved under hypobaric conditions (see Figure). Analysis of brain tissue revealed normal cytoarchitecture in grey matter of the frontal lobe, thalamus, mesencephalon, cerebellum, and medulla. SCAD, known indicators of microvascular injury after embolization, were 56 +/- 15% more numerous and occupied 95 +/- 29% more area in periventricular white matter from control animals compared with those maintained with hypobaric oxygenation ($p<0.001$).

Conclusions: We previously presented that hypobaric oxygenation safely achieves stable gas exchange during CPB in swine while practically eliminating GME delivered to the animal. Here, we describe the mechanism of GME removal by confirming that the sum of partial pressures of dissolved gases in blood is reduced through denitrogenation. Our data confirm that GME removal is enhanced not only in the oxygenator, but also in the arterial filter and in flowing blood of the CPB circuit, consistent with reabsorption of bubbles into the aqueous phase. Histologic data suggest that hypobaric oxygenation preserves grey matter cytoarchitecture in the brain, and may limit end organ microvascular damage. Hypobaric oxygenation is a promising adjunct to arterial filtration for elimination of GME that we hope may improve neurologic outcomes following cardiac surgery.

Oral Presentations

Cognitive Dysfunction and Early Mortality Following Carotid Endarterectomy

Eric J. Heyer, M.D., Ph.D.; Joanna L. Mergeche, B.A.; Joanne Brady, M.S.; Charles J. DiMaggio, Ph.D.; Samuel S. Bruce, M.S.; E. Sander Connolly, M.D.
Columbia University

Background: Cognitive dysfunction is a subtler form of perioperative neurologic injury than stroke. It is observed in approximately 25% of patients undergoing carotid endarterectomy (CEA)1,2. This study aims to determine whether early cognitive dysfunction within 1 day of CEA is associated with increased risk of early mortality compared to patients without cognitive dysfunction.

Methods: Five hundred fifty-one (551) consecutive patients with carotid artery stenosis undergoing elective CEA between 1995 and 2012 were enrolled with written informed consent in this IRB-approved observational study. All patients were evaluated with a battery of neuropsychometric tests for cognitive dysfunction pre-operatively and 1 day post-operatively. Patients with cognitive dysfunction at this time were considered to have early cognitive dysfunction. All patients were followed until 2012. The risk of mortality was assessed using Kaplan-Meier methods and multivariable Cox proportional hazards models.

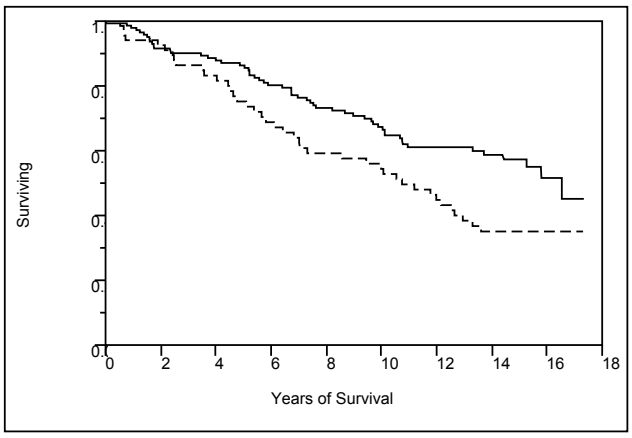
Results: One hundred seventy-eight (178, 32.3%) people died during the study period. The median survival for patients that exhibited cognitive dysfunction within 1 post-operative day was 12.5 years vs. 15.9 years for patients without early cognitive dysfunction (χ^2=2.6, P=0.11). After adjusting for age, diabetes mellitus, and statin use, patients with early cognitive dysfunction had a risk of mortality (adjusted hazard ratio (aHR) 1.23, 95% confidence interval (CI) 0.09–1.69). In stratified multivariable models, patients with early cognitive dysfunction taking statins had an adjusted hazard ratio of 0.88 (95% CI 0.52–1.48). By comparison, patients with early cognitive dysfunction not taking statins had an adjusted hazard ratio of 1.61 (95% CI 1.07–2.42).

Conclusions: This study is the first to demonstrate that early cognitive dysfunction is associated with increased risk of earlier mortality than patients without cognitive dysfunction, particularly in patients not taking statins (Figure 1). This finding validates cognitive dysfunction as an important neurologic outcome, and suggests that preoperative medical management with statins may improve long-term survival.

References:

1. Heyer E, Adams D, Todd G, et al. Neuropsychometric changes in patients after carotid endarterectomy. Stroke; a journal of cerebral circulation. 1998;29(6):1110-1115.
2. Heyer EJ, Sharma R, Rampersad A, et al. A controlled prospective study of neuropsychological dysfunction following carotid endarterectomy. Archives of neurology. Feb 2002;59(2):217-222.

Figure 1. Bivariable Kaplan-Meier Plot – Patients Not Taking Statins.



Oral Presentations

CW 1759-50 An Ultra-Short Acting Nondepolarizer Immediately Antagonized at Any Time by L-Cysteine

John J. Savarese, M.D.[1]; Hiroshi Sunaga, M.D.[1]; Matthew R. Belmont, M.D.[1]; Matthew Murrell, M.D., Ph.D.[1]; Paul M. Heerdt, M.D., Ph.D.[1]; Jeff McGilvra, Ph.D.[2]
Weill Cornell Medical College - New York Presbyterian Hospital[1]; Cedarburg Pharmaceuticals[2]

Background: CW 1759-50 has been developed to reduce histaminoid phenomena in an ultra-short acting nondepolarizer; when compared with gantacurium (GW 280430A) its safety ratio [ED for histaminoid circulatory, pulmonary and cutaneous phenomena/NMB ED95] is approximately four to seven times greater in monkeys and dogs versus that of gantacurium (unpublished data). CW 1759-50 is ultra-short acting because the molecule is inactivated by bodily L-cysteine in a chemical reaction. In this study we tested spontaneous recovery and antagonism of 1759-50 blockade by exogenous L-cysteine at two key points: One minute following a bolus dose of 4x ED95 (0.20 mg/kg) (point A) and one minute following discontinuation of continuous infusions (point B).

Methodology: With IACUC approval male rhesus monkeys weighing 9-18 kg were studied under isoflurane/N2O/O2 anesthesia (1.5-2.0 %); twitch, TOF, blood pressure and heart rate were recorded continuously. Controlled ventilation was maintained and temperature, ETCO2, and SpO2 were kept within normal limits under continuous monitoring. ED95 for NMB was calculated. Neuromuscular function was measured mechanomyographically. Total duration (injection to 95% twitch recovery) following ED95 and 4x ED95 dosage was determined. Continuous infusions of CW 1759-50 were given to monkeys for durations of 30-120 min., where 99-99.5% block was maintained. Rate of spontaneous recovery following infusion was measured as the interval of twitch recovery from 5 to 95 percent twitch height. Intervals [5-95% recovery] following ED95, 4xED95, and infusions were compared.

Reversal of neuromuscular blockade by L-cysteine was measured at two key points: (A) at +1 min after injection of 4x ED95 (0.20 mg/kg); (B) at 100% twitch inhibition 1 min. after cessation of continuous infusion. The [5-95% interval] following L-cysteine reversal was compared with spontaneous recoveries following bolus dosage and infusion.

Results: Rate of spontaneous recovery [5-95% interval] following bolus dosage (1x – 4x ED95) and infusion did not differ. Rate of accelerated recovery (reversal) by L-cysteine also did not differ. (Table).

Discussion: The data indicate that recovery from 1759-50 blockade, whether spontaneous or L-cysteine accelerated (reversal) is unaffected by bolus dosage or infusion. The neuromuscular properties of 1759-50, together with its reduced association with histaminoid phenomena (vis-à-vis gantacurium) suggest that the new compound may present an improved profile in human subjects.

Oral Presentations

NOVA1 Variants Regulate RNA Splicing at The Inhibitory Synapse and Persistent Pain Susceptibility

Roy C. Levitt, M.D.[1]; Yan Ping Zhang, M.D.[1]; Shad Smith, Ph.D.[2]; William Maixner, DDO, Ph.D.[2]; Luda Diatchenko, M.D., Ph.D.[2]; Jian Guo Cui, M.D., Ph.D.[1]; Diana Erasso, Ph.D.[1]; Zhiye Zhuang, Ph.D.[1]; Eden Martin, Ph.D.[1]; Susan Slifer, MS[1]; Eugene S. Fu, M.D.
University of Miami[1]; Algynomics[2]

Introduction: Up to 50% of patients who undergo surgical procedures develop persistent post-operative pain. It is now generally accepted that persistent pain development depends on nerve injury and represents a complex heritable trait (influenced by multiple genes). We hypothesize that susceptibility to persistent pain after peripheral nerve injuries are causally associated with variant genes, and that these genes and the pathways can be identified using functional genomics. In this study, we assessed thermal hyperalgesia over time after peripheral nerve injury in mice, and tested the orthologous human candidate gene for association with susceptibility to persistent pain.

Methods: Post-Op Pain Model of Controlled Nerve Injury: 16 genetically diverse inbred strains of mice were characterized after chronic constriction injury of the sciatic nerve (CCI) for withdrawal latency (seconds) to thermal pain (Hargreaves) at Baseline and Days 1, 7, 14, and 21 after CCI. The area under the withdrawal latency response over time, representing the Persistent Pain Index (PPI), was calculated. Mapping PPI loci: Haplotype Association Mapping (HAM) was conducted to identify genome-wide associations between PPI and 7.8 million single nucleotide polymorphisms (SNP) using ANOVA (as implemented by snpBrowser). In this exploratory study, $P<0.001$ was used to select SNPs associated with thermal responses. We next tried to confirm our HAM results using the Efficient Mixed Models Approach (EMMA). Human association was conducted with genomic DNA from patients with chronic pain and disability due to osteoarthritis (OA). Samples were assayed for SNPs in the NOVA1 gene candidate using Illumina 1M-Duo chips. Association was run with PLINK software.

Results: We observed highly significant differences among inbred strains for thermal hyperalgesia after CCI. HAM identified two loci that contribute to the thermal PPI. One was located on chromosome 5 (at 36 - 36.5 Mb) with 4 transcribed annotated candidate genes within the confidence interval. A second was located on chromosome 12 (at 47.75-47.99 Mb) with one transcribed annotated gene called neurooncologic ventral antigen-1 (Nova1), that encodes a neuron-specific RNA-binding-splicing protein which regulates alternative transcript splicing of multiple genes at the inhibitory synapse. EMMA confirms association at both loci ($P<0.00005$). We next tested whether NOVA1 SNPs were associated with persistent OA pain and disability using the validated WOMAC index score in our large OA population (Table 1). These data demonstrate association with NOVA1 SNPs in the 3' region after adjusting for age, gender, race, and multiple tests.

Discussion: Persistent post-op pain is likely influenced by a small number of genes (oligogenic). Nova1 was identified as one of two loci associated with biologic variability in persistent post-op pain. NOVA1 was independently shown to be associated with persistent pain and disability in a large OA population. Based on these data we speculate that NOVA1 functional variants may explain a maladaptive response to nerve injury across multiple levels of anatomic complexity due to altered synaptic functioning affecting pain processing, perception, and higher-level functions associated with persistent pain.

Program Material

Friday, April 5, 2013

EAB Program (Part 1) Performance Measurement: Does It Matter?

Moderator: Richard P. Dutton, M.D., M.B.A.

Pro: Lee A. Fleisher, M.D.
Con: Avery Tung, M.D., FCCM

EAB Program Part 1: Performance Measurement: Does it Matter?

Background: What Can Be Measured?

Richard P. Dutton, M.D., M.B.A.

As medicine moves into the Information Age the ability for clinicians to understand the broad demographics and outcomes of their work is steadily increasing. With this comes the ability for increased measurement – often externally imposed – of our process and outcomes. In anesthesiology, performance measurement is driven by universal availability of administrative data and increasing penetration of electronic healthcare records. The number of groups with an Anesthesia Information Management System is now 25% of all practices, and close to 60% of academic groups. More than half the remaining groups are under contract, and working to configure and install the software. The next generation of anesthesia residents will emerge from training knowing only electronic record-keeping, and possessed of a misty and sentimental view of paper records as an artifact of the past. Not unlike how many AUA members would regard a copper kettle.

This upheaval of our daily practice has brought with it the potential – largely unrealized – to examine granular clinical data in a systematic fashion. In theory we can learn from examining trends in our practice over time, and comparing our process and outcomes to others. In practice, of course, we MUST learn how to do this in a validated, appropriate and cost effective fashion. Hence the present panel from the EAB, which will pit two giants of quality management in a discussion of the value of performance measurement. Dr. Lee Fleisher, Professor and Chairman at the University of Pennsylvania, will advance the opinion that performance measurement of providers will improve patient care. Dr. Avery Tung, Professor at the University of Chicago, will counter that evidence in favor of performance measurement is scant, and efforts to do so are fraught with technical deficiencies and unintended consequences.

As the moderator of this high-stakes cage match, I will begin by sketching out the current landscape of data collection and reporting. What can we reasonably know about our practice? What are the domains of anesthesia performance measurement, and what are the sources of data? My vantage point is that of Executive Director of the Anesthesia Quality Institute (AQI) and proprietor of the National Anesthesia Clinical Outcomes Registry (NACOR). NACOR is far from the only source of aggregated data in our specialty, but is one example of what can be accomplished. And relentless flacking of AQI participation has provided me with perspective on what data exists and what anesthesia practices are choosing to do with it.

The Good: Certain data about our practice really are universally available. In order to get paid for our services we must generate digital records of what we do. The basic billing file – available for every case, every day, in every practice – includes patient information (age, sex, ASA physical status), facility information (type, location), provider information (names and roles), and information about the case itself (date, time, duration, anesthesia type, surgery and anesthesia CPT codes). The identical data is available from three different sources: the practice that generates it, the software company that records it, and the payor that ultimately receives it. Further, every practice with an AIMS is racking up terabytes of data every month on vital signs, fluids, medications and anesthesia procedures.

Although it would be easy to do, most anesthesia practices do not closely examine this information, even the basic billing records. ASA and other organizations do some work with the annual Medicare files, and Dr. Tremper and MGMA conduct annual surveys, but quantitative aggregation and analysis are surprisingly limited. The good news for our specialty is that NACOR now includes 9,000,000 case records of this type, from more than 13,000 providers at 1400 facilities, which *are* closely examined by the AQI, and are analyzed and reported to our stakeholders. Turning up one's nose at 'administrative data' is common in academic circles, but there is a lot we can learn from this source. In particular, data about our business functions is available and accurate, and it should be easy to report cases done, cases cancelled, on-time starts, average case duration, turn-over times, units billed, and so forth.

The Bad: Of all the practices participating in NACOR, fewer than 25% report on patient outcomes. A larger number collect information at the point of care, but cannot link it to the medical record. To be useful for performance improvement, the knowledge that a given patient had postoperative nausea and vomiting – for example – must be linked to other information like the providers that cared for him and the specific medications received. Even worse, there are no common definitions – especially for minor events – and dozens of different ways to collect the data, each of which influences the results. Comparisons of one provider to another within a practice are often possible, since less risk-adjustment is required if they are treating similar patients in the same facility, but external comparisons are much harder. Despite being our primary goal, we at AQI have been hesitant to push inter-practice benchmarks when the data is shaky – but other external agencies might not be as cautious.

The Ugly: 'Patient-centered outcomes' are all the rage in Washington right now, and are emerging as leading metrics for meaningful use, PQRS, Pay for Performance, and various ACO accreditation plans. Further, the American Board of Medical Specialties is including patient satisfaction metrics in the next round of requirements for Maintenance of Certification, and it's a safe bet the Joint Commission will be close behind. In anesthesiology, we have only a dim view of what a patient-centered metric might be. Patient satisfaction is part of it (and rarely and erratically measured), but 'patient experience' is the broader concept. This might include everything from PONV and pain management to valet parking at the ambulatory surgery center. We are good at safety (major complications in the immediate perioperative period are less than 1/300 in NACOR) and good at efficacy (more than 99% of patients complete the planned procedure), but we will need to go further than this. I observe that despite decades of scientific understanding of PONV risk factors and prophylaxis, few of us actually know how often our patients throw up on the way home from the Surgicenter. Of the 250 practices that AQI communicates with right now, no more than 3 or 4 have any kind of performance data that would be considered 'patient centered' and even these groups are not quite sure what to do with it.

With that background established, let the debate begin!

Pro: EAB Program (Part 1) Performance Measurement: Does It Matter?

Lee A. Fleisher, M.D.

We are in the midst of major changes in the healthcare delivery system and it is critical that anesthesiologists need to be involved. As part of the Affordable Care Act, the U.S. Department of Health and Human Services (HHS) was required to develop a National Strategy for Quality Improvement in Health Care (National Quality Strategy). The Center for Medicare and Medicaid Services (CMS) has identified the triple aim: 1) better care for individuals, 2) better health for populations and 3) lower costs. In order to achieve the triple aim, the strategy established six priorities. Those priorities are:

Making care safer by reducing harm caused in the delivery of care. Ensuring that each person and family is engaged as partners in their care.

- Promoting effective communication and coordination of care.
- Promoting the most effective prevention and treatment practices for the leading causes of mortality, starting with cardiovascular disease.
- Working with communities to promote wide use of best practices to enable healthy living.
- Making quality care more affordable for individuals, families, employers, and governments by developing and spreading new health care delivery models.

It is within this context that the National Quality Forum (NQF, www.qualityforum.org), a non-profit private-public collaboration, has been tasked to endorse and maintain national consensus standards for measuring and publicly reporting on performance. Given these priorities, understanding the direction of efforts at NQF and where performance measurement is going more broadly is of tremendous importance to practicing Anesthesiologists.

The evidence on pay-for-performance for the relationship between adherence to process measures and outcomes is mixed. Werner and Bradlow performed a cross-sectional study of hospital care between January 1 and December 31, 2004, for acute myocardial infarction, heart failure, and pneumonia at acute care hospitals in the United States included in the Hospital Compare Web site and compared them with hospital risk-adjusted mortality rates, which were measured using Medicare Part A claims data. Across all acute myocardial infarction performance measures, the absolute reduction in risk-adjusted mortality rates between hospitals performing in the 25th percentile *versus* those performing in the 75th percentile was 0.005 for inpatient mortality, 0.006 for 30-day mortality, and 0.012 for 1-yr mortality. They concluded that hospital performance measures predict small differences in hospital risk-adjusted mortality rates and that effort should be made to develop performance measures that are tightly linked to patient outcomes.

Lindenauer and colleagues measured changes in adherence to 10 individual and 4 composite measures of quality over a period of 2 years at 613 hospitals that voluntarily reported information about the quality of care through a national public-reporting initiative, including 207 facilities that simultaneously participated in a pay-for-performance demonstration project funded by the Centers for Medicare and Medicaid Services.(1) Hospitals engaged in both public reporting and pay for performance achieved modestly greater improvements in quality than did hospitals engaged only in public reporting.

Recently, Sutton and colleagues reported on 30-day in-hospital mortality among 134,435 patients admitted for pneumonia, heart failure, or acute myocardial infarction to 24 hospitals covered by the pay-for-performance program in England.(2) Risk-adjusted, absolute mortality for the conditions included in the pay-for-performance program decreased significantly, with an absolute reduction of 1.3 percentage points and a relative reduction of 6%. The authors concluded that the introduction of pay for performance in one region of England was associated with a clinically significant reduction in mortality. As compared with a similar U.S. program, the U.K. program had larger bonuses and a greater investment by hospitals in quality-improvement activities.

Currently, only processes of care have been the focus of anesthesia metrics. Specifically, the Surgical Care Improvement Project (SCIP) is part of the current hospital-based pay-for performance (P4P) value-based purchasing.

The evidence regarding the value of SCIP has been negative to date. Stulberg and colleagues performed a retrospective cohort study, using Premier Inc's Perspective Database for discharges between July 1, 2006 and March 31, 2008.(3) Adherence measured through a global all-or-none composite infection-prevention score was associated with a lower probability of developing a postoperative infection. However, adherence reported on individual SCIP measures, which is the only form in which performance is publicly reported, was not associated with a significantly lower probability of infection.

Ingraham and colleagues performed a cross-sectional study of hospitals participating in the ACS NSQIP and SCIP.(4) American College of Surgeons' National Surgical Quality Improvement Project (NSQIP) outcomes (30-day overall morbidity, serious morbidity, surgical site infections [SSI], and mortality) and adherence to SCIP SSI-related process measures (from the Hospital Compare database) were collected from January 1, 2008, through December 31, 2008. Better adherence to infection-related process measures over the observed range was not significantly associated with better outcomes with one exception, correct antibiotic (SCIP-Inf2) and surgical site infections.

Bratzler and colleagues analyzed SCIP data on fee-for-service Medicare patients aged > 65 years for 1,638,756 cases from 2007-2009.(5) With the exception of the hair removal measure, eligible patients who passed the SCIP infection measures had better outcomes including fewer surgical infections as compared to patients who did not pass the measures. Patients excluded from SCIP measures had much worse outcomes.

Prominent surgical organizations have demonstrated a clear movement toward outcome measures. There are numerous surgical outcome measures developed using risk-adjustment methodology including those developed for the American College of Surgeons' National Surgical Quality Improvement Project (NSQIP) and the Society of Thoracic Surgeons (STS). These include risk-adjusted measures of cardiac

surgery mortality and complications such as renal failure. Future research will focus on the ability to develop joint accountability outcome measures with our surgical colleagues.

References

1. Lindenauer PK, Remus D, Roman S, Rothberg MB, Benjamin EM, Ma A, et al. Public reporting and pay for performance in hospital quality improvement. The New England journal of medicine. 2007 Feb 1;356(5):486-96. PubMed PMID: 17259444.
2. Sutton M, Nikolova S, Boaden R, Lester H, McDonald R, Roland M. Reduced mortality with hospital pay for performance in England. The New England journal of medicine. 2012 Nov 8;367(19):1821-8. PubMed PMID: 23134382.
3. Stulberg JJ, Delaney CP, Neuhauser DV, Aron DC, Fu P, Koroukian SM. Adherence to surgical care improvement project measures and the association with postoperative infections. JAMA : the journal of the American Medical Association. 2010 Jun 23;303(24):2479-85. PubMed PMID: 20571014.
4. Ingraham AM, Cohen ME, Bilimoria KY, Dimick JB, Richards KE, Raval MV, et al. Association of surgical care improvement project infection-related process measure compliance with risk-adjusted outcomes: implications for quality measurement. Journal of the American College of Surgeons. 2010 Dec;211(6):705-14. PubMed PMID: 21109157.
5. Bratzler D, Ma A, Nsa W, Baus K, Rapp M, Fleisher L, et al. Performance on SCIP Measures and Risk of Surgical Site Infection. Proceedings of Infectious Disease Society of America Annual Meeting. 2011.

Con: EAB Program (Part 1) Performance Measurement: Does It Matter?

Avery Tung, M.D., FCCM

Notes: _____

Performance measurement?

(The devil is in the details)

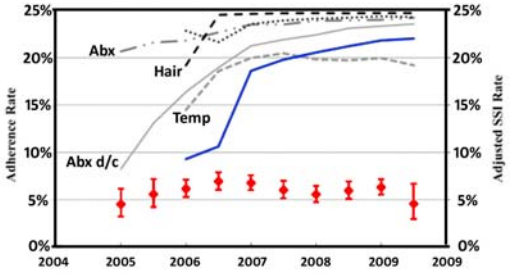
Avery Tung, M.D.
Quality Chief for Anesthesia
Department of Anesthesia and Critical Care
University of Chicago

Surgical Site Infection Prevention

Time to Move Beyond the Surgical Care Improvement Program

Mary T. Hawn, MD, MPH,† Catherine C. Vick, MS,* Joshua Richman, MD, PhD,*† William Holman, MD,*† Rhiannon J. Deierhoi, MPH,* Laura A. Graham, MPH,* William G. Henderson, MPH, PhD,‡ and Kamal M.F. Itani, MD§*

60,853 surgeries in 112 VA hospitals



Ann Surg 2011;254:494–501

ORIGINAL CONTRIBUTION

Association Between Performance Measures and Clinical Outcomes for Patients Hospitalized With Heart Failure

Gregg C. Fonarow, MD
William T. Abraham, MD
Nancy M. Albert, RN, PhD
Wendy Gattis Stough, PharmD
Mihai Gheorghiade, MD
Barry H. Greenberg, MD
Christopher M. O'Connor, MD
Karen Pieper, MS
Jie Lena Sun, MS
Clyde Yancy, MD
James B. Young, MD
for the OPTIMIZE-HF Investigators and Hospitals

Hospital compliance with performance measures and 30-day outcomes in patients with heart failure

David W. Schopfer, MD,[a] Mary A. Whooley, MD,[b,c,d] and Thomas D. Stamos, MD[a] *Chicago, IL; and San Francisco, CA*

Relationship Between Leapfrog Safe Practices Survey and Outcomes in Trauma

Laurent G. Glance, MD; Andrew W. Dick, PhD; Turner M. Osler, MD; J. Wayne Meredith, MD; Patricia W. Stone, PhD; Yue Li, PhD; Dana B. Mukamel, PhD

No relationship!

Arch Surg 2011;146:1170-7

Adherence to Surgical Care Improvement Project Measures and the Association With Postoperative Infections

Jonah J. Stulberg, MD, PhD, MPH
Conor P. Delaney, MD, PhD
Duncan V. Neuhauser, PhD
David C. Aron, MD, MS
Pingfu Fu, PhD
Siran M. Koroukian, PhD

No association with measure performance!

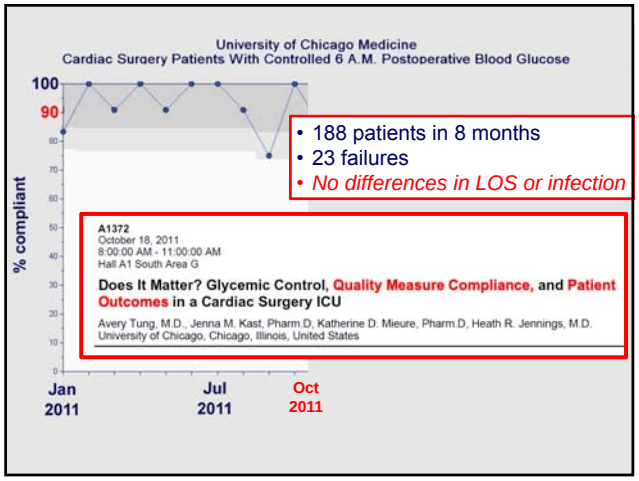
Arch Surg 2011;146:1170-7

Surgical Care Improvement Should Performance Measures Have Performance Measures

Mary T. Hawn, MD, MPH

"It appears that investing resources in SCIP reporting is ***no longer cost effective***"

JAMA 2010;303:2527-8

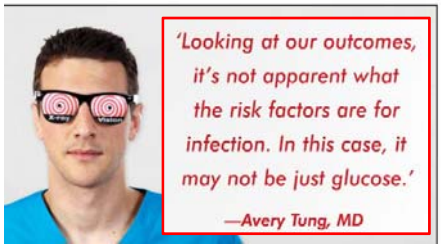


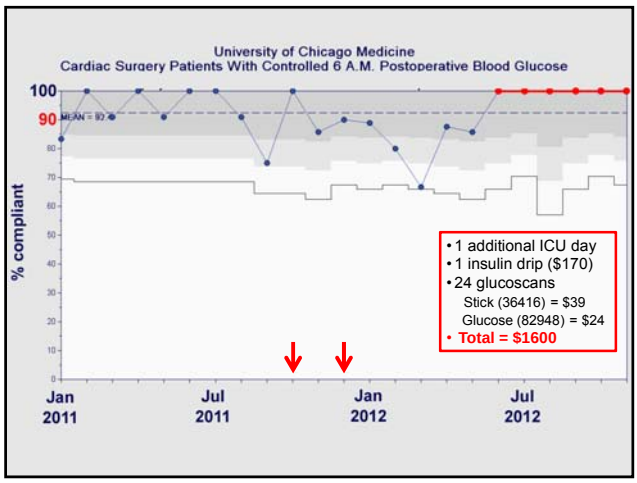
Anesthesiology News, 12/2011

CLINICAL ANESTHESIOLOGY

Results for Glucose Control in Cardiac ICU Not All Sweet

The University of Chicago Experience





Relevance of the Surgical Care Improvement Project on glycemic control in patients undergoing cardiac surgery who receive continuous insulin infusions

Marie E. McDonnell, MD,[a] Sara M. Alexanian, MD,[a] Ana Junqueira, MD,[a] Howard Cabral, PhD,[b] and Harold L. Lazar, MD[c]

- 832 patients s/p cardiac surgery
- 55 SCIP Inf-4 failures (6.6%)

TABLE 3. Postoperative outcomes

Variable	SCIP outlier (n = 55)	SCIP compliant (n = 777)	*P* value
Thirty-day mortality (%)	1 (1.8)	13 (1.7)	.55
Myocardial infarction (%)	1 (1.8)	11 (1.4)	.52
Permanent stroke (%)	1 (1.8)	7 (0.9)	.39
Deep sternal infection (%)	0 (0)	3 (0.4)	1.00
Ventilatory support > 24 h (%)	5 (9.0)	52 (6.7)	.38
Multisystem failure (%)	1 (1.8)	7 (0.9)	.43
Atrial fibrillation (%)	9 (16.3)	235 (30.3)	.05
Hospital length of stay	11.69 ± 11.02	9.75 ± 7.83	.20

J Thorac Cardiovasc Surg 2013;145:590-7

Health Services and Outcomes Research

Racial Profiling

The Unintended Consequences of Coronary Artery Bypass Graft Report Cards

Rachel M. Werner, MD, PhD; David A. Asch, MD, MBA; Daniel Polsky, PhD

"The increased racial and ethnic disparities after CABG report cards resulted in 19% fewer CABG surgeries among Black and Hispanic patients in New York"

Circulation 2005;111:1257-63

Medicare's Policy to Limit Payment for Hospital-Acquired Conditions: The Impact on Safety Net Providers*

Megan McHugh, PhD
Timothy C. Martin, PhD
John Orwat, PhD
Kevin Van Dyke, MPP

	Number of Discharges	HACs Rate Per 1,000 Medicare Admissions		
	All Hospitals (n=3,623)	Safety Net Hospitals (n=500)	Non-Safety Net Hospitals (n=2,704)	All Hospitals (n=3,623)
All Conditions	476,275	65.54***	57.61	57.93
Pressure ulcers (III/IV)	242,039	35.10***	29.40	30.38
Falls and trauma	205,000	26.59*	24.87	24.26
Poor glycemic control	14,655	2.34***	1.67	1.73
Catheter associated UTI	8,812	1.03	1.07	0.99
DVT and PE	4,433	0.34**	0.45	0.43

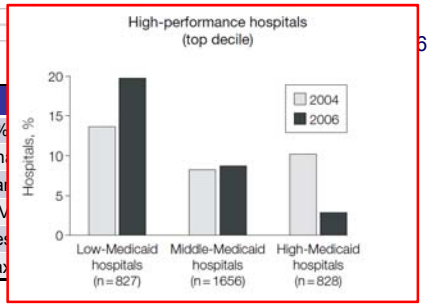
*Medicare caseload>1Stdev

J Health Care Poor Underserved 2011;22:638-47

ORIGINAL CONTRIBUTION

Comparison of Change in Quality of Care Between Safety-Net and Non–Safety-Net Hospitals

Rachel M. Werner, MD, PhD
E. Elizabeth Goldman, MD, MCR
R. Adams Dudley, MD, MBA



Medicaid %
ASA (disch
BB (dischar
ACEI for LV
LVEF asses
Pneumovax

*all p<0.05

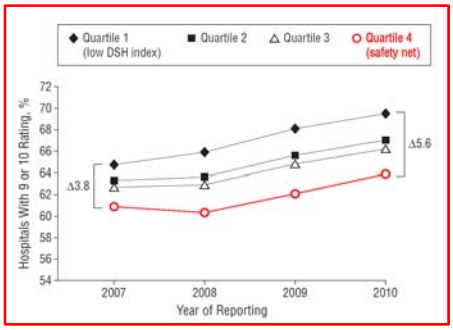
JAMA 2008;299:2180-7

HEALTH CARE REFORM

Patient Experience in Safety-Net Hospitals

Implications for Improving Care and Value-Based Purchasing

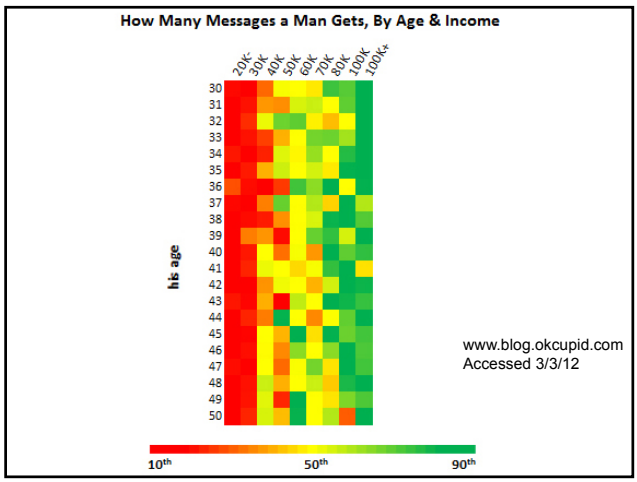
Paula Chatterjee, MPH; Karen E. Joynt, MD, MPH; E. John Orav, PhD; Ashish K. Jha, MD, MPH



DSH = "disproportionate share hospital"
Rating = HCAHPS component of VBS program

Arch Intern Med 2012;172:1204-10

Fog of war


How Many Messages a Man Gets, By Age & Income
20K-
30K
40K
50K
60K
70K
80K
100K
100K+
his age
30
31
32
33
34
35
36
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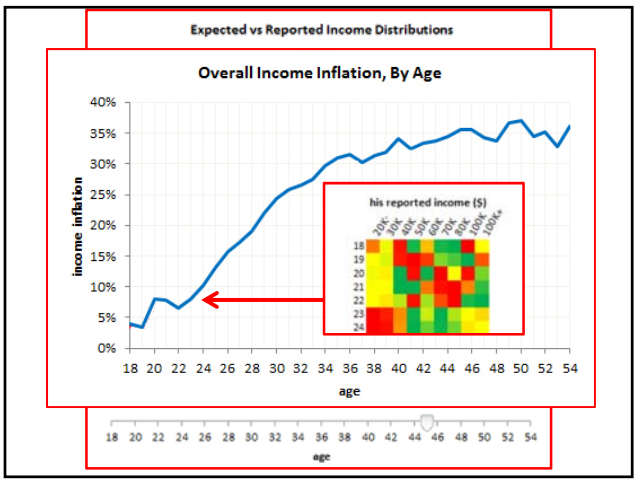
10th
50th
90th
www.blog.okcupid.com
Accessed 3/3/12


Expected vs Reported Income Distributions
Overall Income Inflation, By Age
income inflation
40%
35%
30%
25%
20%
15%
10%
5%
0%
18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54
age
his reported income ($)
20K-
30K
40K
50K
60K
70K
80K
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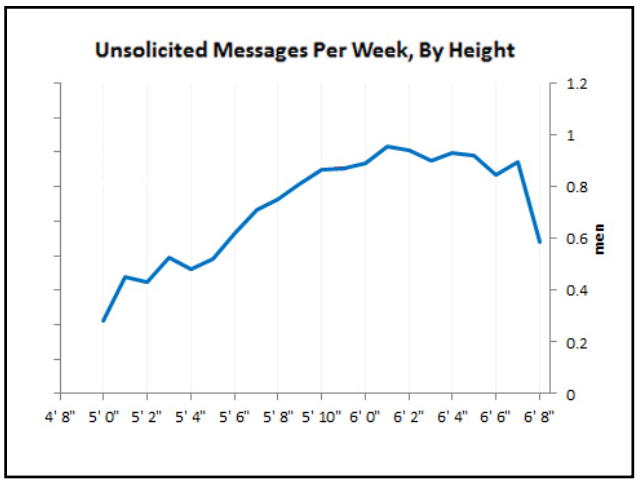
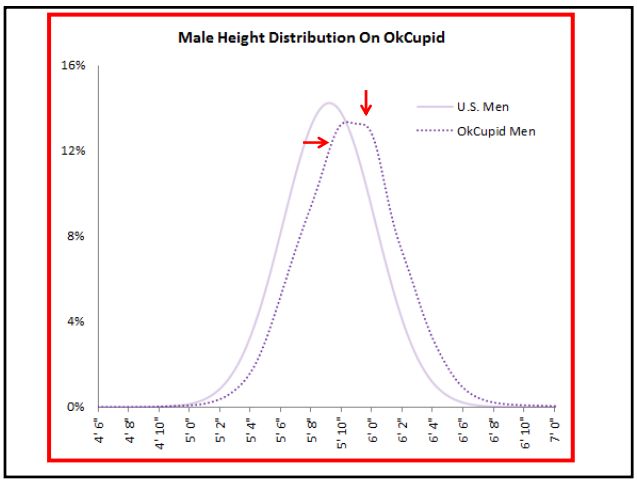
23
24
18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54
age

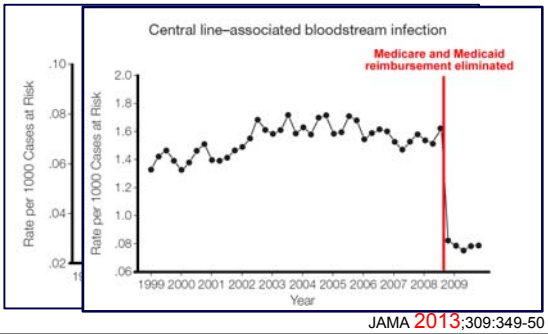

Unsolicited Messages Per Week, By Height
men
1.2
1
0.8
0.6
0.4
0.2
0
4' 8" 5' 0" 5' 2" 5' 4" 5' 6" 5' 8" 5' 10" 6' 0" 6' 2" 6' 4" 6' 6" 6' 8"


Male Height Distribution On OkCupid
16%
12%
8%
4%
0%
U.S. Men
OkCupid Men
4' 6" 4' 8" 4' 10" 5' 0" 5' 2" 5' 4" 5' 6" 5' 8" 5' 10" 6' 0" 6' 2" 6' 4" 6' 6" 6' 8" 6' 10" 7' 0"

Tension Between Quality Measurement, Public Quality Reporting, and Pay for Performance

Steven A. Farmer, MD, PhD
Bernard Black, MA, JD
Robert O. Bonow, MD, MS

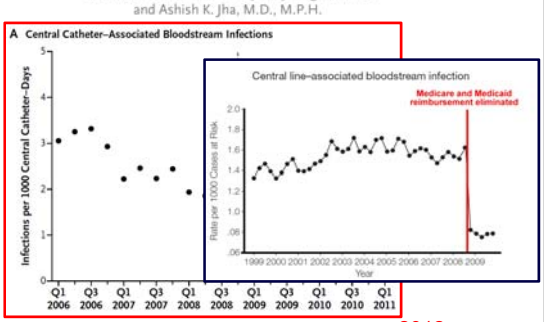
NIS data review
1999-2009



JAMA 2013;309:349-50

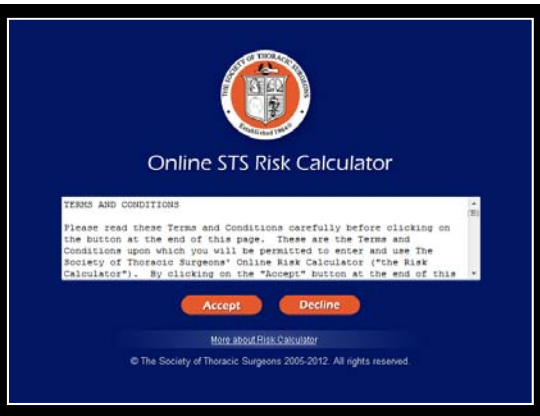
Effect of Nonpayment for Preventable Infections in U.S. Hospitals

Grace M. Lee, M.D., M.P.H., Ken Kleinman, Sc.D., Stephen B. Soumerai, Sc.D., Alison Tse, Sc.D., David Cole, B.M., Scott K. Fridkin, M.D., Teresa Horan, M.P.H., Richard Platt, M.D., Charlene Gay, B.A., William Kassler, M.D., M.P.H., Donald A. Goldmann, M.D., John Jernigan, M.D., and Ashish K. Jha, M.D., M.P.H.



398 hospitals, NHSN data, 2006-2011

N Engl J Med 2012;367:1428-37



"Methodology as solid as it gets"
-R. Dutton, MD, MBA

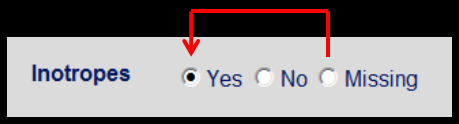
A 72 yr 5'9" 80 kg M s/f AVR

Calculations	
Procedure Name	Isolated AVRepl
Risk of Mortality	0.874%
Morbidity or Mortality	9.098%
Long Length of Stay	2.913%
Short Length of Stay	58.231%
Permanent Stroke	0.865%
Prolonged Ventilation	4.118%
DSW Infection	0.220%
Renal Failure	1.523%
Reoperation	6.164%

Calculations	
Procedure Name	Isolated AVRepl
Risk of Mortality	1.616%
Morbidity or Mortality	16.414%
Long Length of Stay	5.061%
Short Length of Stay	40.007%
Permanent Stroke	0.865%
Prolonged Ventilation	7.862%
DSW Infection	0.370%
Renal Failure	2.928%
Reoperation	6.988%

STS data element 1790: Medinotr

"Indicate whether the patient received IV inotropic agents within 48 hours preceding surgery"



Δ=1.1%

Avery, you lie! How can you not know whether the patient was on inotropes or not?

EDITORIAL VIEWS

Anesthesiology 2008; 108:973–4

Dobutamine

Too Dangerous for "Routine" Administration?

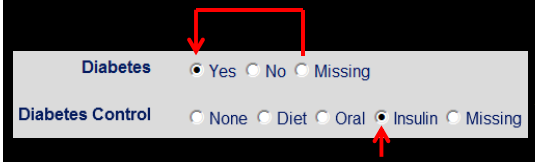
"Depending on the center in which the surgery takes place, PIDs* may be administered to as few as 5% or to as many as 100% of patients undergoing elective coronary artery bypass surgery"

*positive inotropic drugs

Anesthesiology 2008;108:973-4

STS data element 780: Diabetes

"Capture the presence and or history of diabetes*, regardless of duration of disease or need for anti-diabetic agents diagnosed prior to surgical intervention"



Δ0.9%

* $A_1C > 6.5\%$
FPG ≥ 126 mg/dl
GTT ≥ 200 mg/dl
Diabetes Care 2010;33:S11-61

"160! We'd better put him on a sliding scale"

Undiagnosed diabetes—data from the English longitudinal study of ageing

M. B. Pierce, P. Zaninotto, N. Steel* and J. Mindell

18.5% undiagnosed

Diabet Med 2009;26:679-85

High prevalence of undiagnosed diabetes mellitus in Southern Germany: Target populations for efficient screening. The KORA survey 2000

W. Rathmann[1], B. Haastert[1], A. Icks[1], H. Löwel[2], C. Meisinger[2], R. Holle[2], G. Giani[1]

40% undiagnosed

Diabetologia 2003;46:182-9

Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study

Anna Norhammar, Åke Tenerz, Göran Nilsson, Anders Hamsten, Suad Efendic, Lars Rydén, Klas Malmberg

Incidence of diabetes:
- **31%** at discharge
- **25%** at 3 months

Lancet 2002; 359: 2140-44

ORIGINAL ARTICLE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

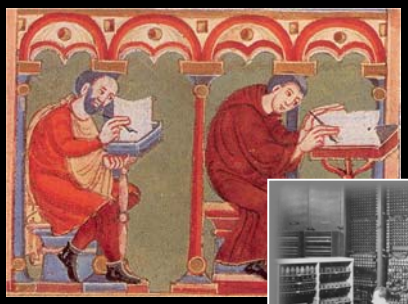
11,140 Type II DM patients
"intensive" vs standard control*
No difference in mortality or CV events

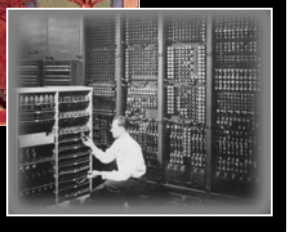
	Baseline	End of Study
Intensive control	1.5%	40.5%
Standard control	1.4%	24.1%

*HbA1C < 6.5 vs. < 7.3

N Engl J Med 2008;358:2560-72.

So we'll just use good clinical data!





Which we can get from the EMR to make it easier…

The New York Times

November 22, 2012

A Shortcut to Wasted Time

By LEORA HORWITZ

New Haven

A FEW years ago, we doctors kept handwritten charts about patients. Back then, it sometimes seemed like we spent half our time walking around looking for misplaced charts, and the other half trying to decipher the handwriting when we found them. The upside was that if I did have the chart in front of me, and I saw that someone had taken the trouble to write something down, I believed it.

"I've seen "*patient is on day two of antibiotics*" appear for 5 days in a row on one chart"

http://www.nytimes.com/2012/11/23/opinion/shortcuts-in-medical-documentation.html?_r=0
Accessed 3/2/13

Assessing the Validity of National Quality Measures for Coronary Artery Disease Using an Electronic Health Record

Stephen D. Persell, MD, MPH; Jennifer M. Wright, MD; Jason A. Thompson, BA; Karen S. Kmetik, PhD; David W. Baker, MD, MPH

Automated (EPIC) reporting vs manual chart review for CAD-related quality measure performance

Quality Measure	Quality Failures by Automated Criteria, No.	Failures Meeting Measure Criteria on Review, No.	Failures Meeting Exclusion Criteria on Review, No.	Rate of Misclassification, %
Antiplatelet drug	120	38	59	81
Lipid-lowering drug	67	5	38	64
β-Blocker after MI	23	1	10	48
Blood pressure measured	24	11	8	79
Lipid measurement	185	16	55	38
LDL-C control	121	0*	18	15†
ACE inhibitor/ARB	42	4	10	33

Arch Intern Med 2006;166:2272-77

Electronic Health Records and the Reliability and Validity of Quality Measures: A Review of the Literature

35 studies

Kitty S. Chan,[1] Jinnet B. Fowles,[2] and Jonathan P. Weiner[1]

- 12-71% documentation of comorbidites in problem lists
- 28-76% of free-text information captured in structured fields

"Given these findings, the data quality from these sources must improve significantly before they can be used for quality reporting"

Med Care Res Rev 2010;67:503-27

Accuracy of Electronically Reported "Meaningful Use" Clinical Quality Measures

A Cross-sectional Study

Lisa M. Kern, MD, MPH; Sameer Malhotra, MD, MA; Yolanda Barrón, MS; Jill Quaresimo, RN, JD; Rina Dhopeshwarkar, MPH; Michelle Pichardo, MPH; Alison M. Edwards, MStat; and Rainu Kaushal, MD, MPH

Single system comparison of electronic and manual documentation of 12 quality measures

	EMR (%)	Manual (%)
Appropriate asthma medication	38	77
Breast CA screening	26	33
LDL cholesterol <100mg/dl	57	37
Flu vaccine	35	30
DVT prophylaxis	75	65
Pneumovax	27	48

Ann Intern Med 2013;158:77-83

The ultimate fog

(Do you see a musician or a woman's face?)

The Limited Value of Sequencing Cases Based on Their Probability of Cancellation

Avery Tung, MD,* Franklin Dexter, MD, PhD,† Sharon Jakubczyk, RN,* and David B. Glick, MD, MBA*

946 cancellations* over 12 months

A patients is scheduled for outpatient surgery early in the day. Because of equipment delay she waits most of the day and then tells her surgeon to cancel because she does not want to wait longer

Whose fault is the cancellation?

a. The patient (who doesn't want to wait any longer)?
b. The surgeon (who does the cancelling)?
c. The hospital (that caused the delay)?

*28% were ambiguous!

Anesth Analg 2010;111:749–56

A 78 yr F is found unresponsive 6 hours after Hysterectomy

- 90 minutes ago, her narcotic-containing epidural was increased from 4 to 7cc/hr for pain
- Hypotensive (76/40) with HR 75
- ABG: 7.16/68/76 on 40% FiO_2 and Hb = 8 (10 postop)
- Abdomen is distended

Is this a narcotic-induced respiratory arrest?

"I think the Ravens are gonna regret this"

ScottB

"Can't say he didn't earn it!"

ChadA

sports.yahoo.com
3/2/2013

Forbes · New Posts (+2 posts this hour) · Most Popular (Most Miserable Cities) · Lists (Hedge Fund Billionaires)

Joe Flacco To Become Highest Paid Player In NFL History*

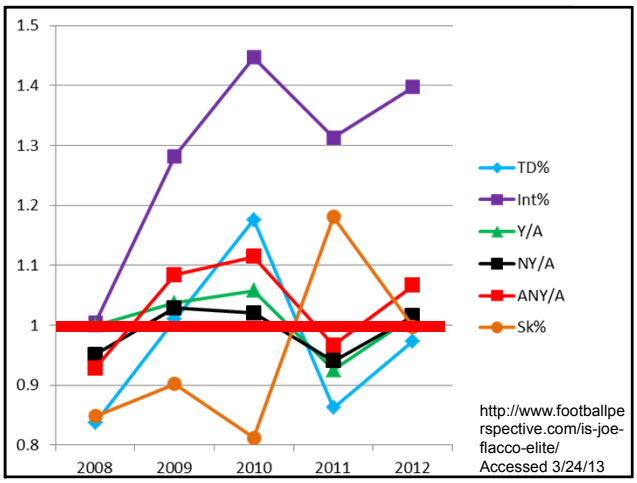
7 comments, 7 called-out + Comment Now + Follow Comments

Apparently Joe Flacco did see Tom Brady's new contract.

*20.1M/year

Fox Sports is reporting that the Baltimore Ravens 28 year old quarterback is set to sign a deal valued at $120.6 million over six years, better than $20 million a season, making the reigning Super Bowl MVP the highest paid player in the history of football.

www.forbes.com, accessed 3/2/13



http://www.footballperspective.com/is-joe-flacco-elite/ Accessed 3/24/13

How much would you pay?

$20M/yr

???

	Manning (20M)	Flacco (20.1M)
ANY/A (index)	126	105
NY/A (index)	122	101
Sack (%) (index)	123	101
Completion % (index)	127	97
Super Bowls	*1*	*1*

*100 = average
Mean 2012 salary = $9.8M
Median = $10.25M
Stdev = $4.6M

www.pro-football-reference.com 2012 data

ORIGINAL INVESTIGATION

The Cost of Satisfaction

A National Study of Patient Satisfaction, Health Care Utilization, Expenditures, and Mortality

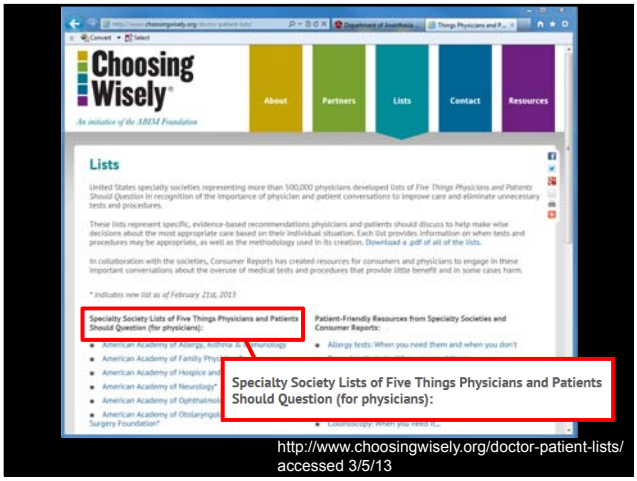
Joshua J. Fenton, MD, MPH; Anthony F. Jerant, MD; Klea D. Bertakis, MD, MPH; Peter Franks, MD

Retrospective review of CAHPS* and MEPS** databases, 2000-2005

	HR for mortality All patients (N = 36,428)	HR for mortality Excluding poor objective and self-related health (N=30,674)
1 (Least satisfied)	1	1
2	1.08	1.17
3	1.02	1.16
4 (Most satisfied)	1.26***	1.44***

*Consumer Assessment of Health Plans
**Medical Expenditure Panel Survey
***p<0.02

Arch Intern Med 2012;172:405-11



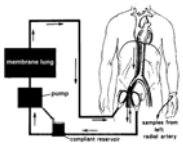
http://www.choosingwisely.org/doctor-patient-lists/ accessed 3/5/13

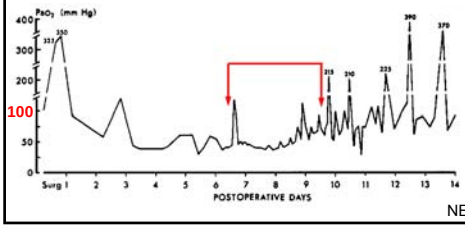
PROLONGED EXTRACORPOREAL OXYGENATION FOR ACUTE POST-TRAUMATIC RESPIRATORY FAILURE (SHOCK-LUNG SYNDROME)

Use of the Bramson Membrane Lung

J. Donald Hill, M.D., Thomas G. O'Brien, M.D., James J. Murray, M.D., Leon Dontigny, M.D., M. L. Bramson, A.C.G.I., J. J. Osborn, M.D., and F. Gerbode, M.D.

- 24 yr M with ARDS after MVA
- Discharged on POD #56





NEJM 1972;286:629-34

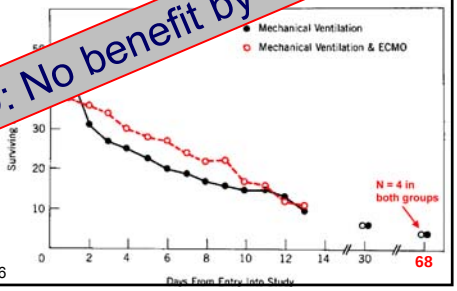
Extracorporeal Membrane Oxygenation in Severe Acute Respiratory Failure

A Randomized Prospective Study

Warren M. Zapol, MD; Michael T. Snider, MD; Hill, MD; Robert J. Fallat, MD; Robert H. Bartlett, MD; L. Henry Ed ris, MD; E. Converse Peirce II, MD; Arthur N. Thomas, MD; Herbe Drinker, PhD; Philip C. Pratt, MD; ert G. Miller, Jr, PhD

ECMO: No benefit by PRCT!

90 hypoxemic patients* randomi ECM conve ventila on



JAMA 1979;242:2193-6

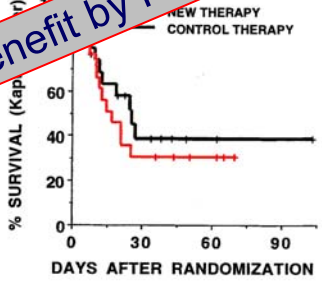
Randomized Clinical Trial of Pressure-controlled Inverse Ratio Ventilation and Extracorporeal CO_2 Removal for Adult Respiratory Distress Syndrome

ALAN H. MORRIS, C. JANE WALLACE, RONALD L. MENLOVE†, TERRY P. CLEMMER, JAMES F. ORME, JR., LINDELL K. WEAVER, NATHAN C. DEAN, FRANK THOMAS, THOMAS D. EAST, NATHAN L. P... MARY R. SUCHYTA, EDUARDO BECK, MICHELA BOMBINO, DEAN F. SITTIG, STEPHAN ... BARBARA HOFFMANN, HAYO BECKS, SAMUEL BUTLER, JAMES PEARL, and BRAD...

40 patients with hypoxemic respiratory failure

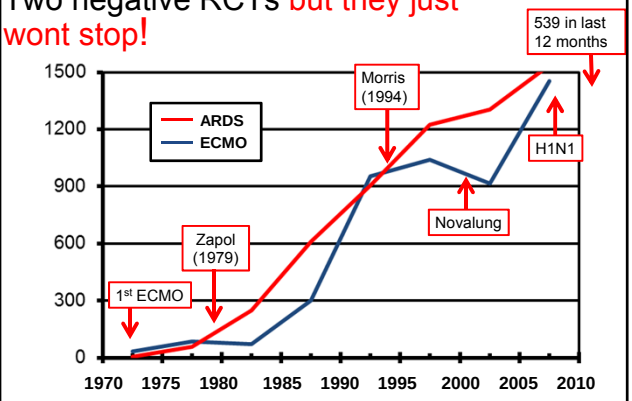
Stopped e... mor... group (70 ...)

ECMO: No benefit by PRCT!



AJRCCM 1994;149:295-305

Two negative RCTs but they just wont stop!



Pubmed citations for ARDS and ECMO, 1970-2010 in 5 year increments
www.pubmed.com, accessed Oct 7, 2012

Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial

Giles J Peek, Miranda Mugford, Ravindranath Tiruvoipati, Andrew Wilson, Elizabeth Allen, Mariamma M Thalanany, Clare L Hibbert, Ann Truesdale, Felicity Clemens, Nicola Cooper, Richard K Firmin, Diana Elbourne, for the CESAR trial collaboration

180 patients randomized to ECMO* or conventional ventilation

90 control patients
- 53% died

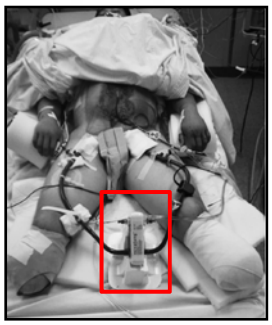
90 ECMO patients**
- 37% died

*Via referral to ECMO center
**24 did not get ECMO and 5/24 (21%) died

Lancet 2009;374:1351-63

From Baghdad to Germany: Use of a New Pumpless Extracorporeal Lung Assist System in Two Severely Injured US Soldiers

MARKUS ZIMMERMANN,* ALOIS PHILIPP,† FRANZ-XAVER SCHMID,† WARREN DORLAC,‡ MATTHIAS ARLT,* AND THOMAS BEIN*



ASAIO Journal 2007;53:e4-e6

Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

Juliana Barr, MD, FCCM[1]; Gilles L. Fraser, PharmD, FCCM[2]; Kathleen Puntillo, RN, PhD, FAAN, FCCM[3]; E. Wesley Ely, MD, MPH, FACP, FCCM[4]; Céline Gélinas, RN, PhD[5]; Joseph F. Dasta, MSc, FCCM, FCCP[6]; Judy E. Davidson, DNP, RN[7]; John W. Devlin, PharmD, FCCM, FCCP[8]; John P. Kress, MD[9]; Aaron M. Joffe, DO[10]; Douglas B. Coursin, MD[11]; Daniel L. Herr, MD, MS, FCCM[12]; Avery Tung, MD[13]; Bryce R. H. Robinson, MD, FACS[14]; Dorrie K. Fontaine, PhD, RN, FAAN[15]; Michael A. Ramsay, MD[16]; Richard R. Riker, MD, FCCM[17]; Curtis N. Sessler, MD, FCCP, FCCM[18]; Brenda Pun, MSN, RN, ACNP[19]; Yoanna Skrobik, MD, FRCP[20]; Roman Jaeschke, MD[21]

a. We recommend either daily sedation interruption or a light target level of sedation be routinely used in mechanically ventilated adult ICU patients (+1B).

Crit Care Med 2013;41:263-306

Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation

J. P. Kress, A. S. Pohlman, M. F. O'Connor, and J. B. Hall

Abstract | Full Text | PDF

DSI group had fewer:

- Ventilator days (4.9 vs 7.3)
- ICU days (6.4 vs 9.9)
- CT scans (9 vs 27)

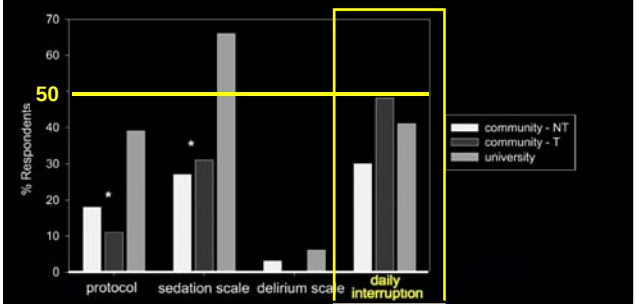
NO difference in complications

NEJM 2000;342:1471-7

Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients*

Sangeeta Mehta, MD; Lisa Burry, PhD; Sandra Fischer, MD; J. Carlos Martinez-Motta, MD; David Hallett, MSc; Dennis Bowman, BSc; Cindy Wong, PhD; Maureen O. Meade, MD, MSc; Thomas E. Stewart, MD; Deborah J. Cook, MD, MSc; for the Canadian Critical Care Trials Group

Crit Care Med 2006;34:374-80



Current Practices in Sedation and Analgesia for Mechanically Ventilated Critically Ill Patients

A Prospective Multicenter Patient-based Study

Jean-Francois Payen, M.D., Ph.D., Gérald Chanques, M.D.,† Jean Mantz, M.D., Ph.D.,‡ Christiane Hercule, M.D.,§ Igor Auriant, M.D.,‖ Jean-Luc Leguillou, M.D.,# Michèle Binhas, M.D.,** Céline Genty, B.Sc.,†† Carole Rolland, B.Sc.,‡‡ Jean-Luc Bosson, M.D., Ph.D.§§ for the DOLOREA Investigators‖‖*

1,381 patients in 43 French ICUs

NO SITE (0%) WAS USING DSI!!!

Anesthesiology 2007;106:687–95

Imagine you're an ICU nurse…

- You initiate DSI in bed #4
  - A 22 yo 100kg gangster with PCP overdose
- You begin a bedding change in bed #6
- During the roll, the resident shows up to inspect for decubiti
- He/she asks to quickly do a biopsy…
- Your gangster self-extubates and codes
  - An incident report is written

Will you DSI bed 4 tomorrow?

Research Open Access

Randomized trial comparing daily interruption of sedation and nursing-implemented sedation algorithm in medical intensive care unit patients

Marjolein de Wit[1], Chris Gennings[2], Wendy I Jenvey[1] and Scott K Epstein[3]

268 MICU patients randomized to DSI or control:

Results:
- DSI protocol amended after 3 study related adverse events
- 4 DSI patients withdrawn at the request of the family
- DSI: ↑ mortality, Longer MV duration, ICU and hospital LOS
- *Study terminated after 74 patients*

Critical Care 2008;12:R70

Daily Sedation Interruption in Mechanically Ventilated Critically Ill Patients Cared for With a Sedation Protocol

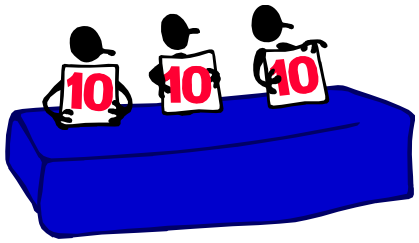
A Randomized Controlled Trial

Sangeeta Mehta, MD
Lisa Burry, PharmD
Deborah Cook, MD
Dean Fergusson, PhD
Marilyn Steinberg, RN
John Granton, MD
Margaret Herridge, MD
Niall Ferguson, MD
John Devlin, PharmD
Maged Tanios, MD
Peter Dodek, MD
Robert Fowler, MD
Karen Burns, MD
Michael Jacka, MD
Kendiss Olafson, MD
Yoanna Skrobik, MD
Paul Hébert, MD
Elham Sabri, MSc
Maureen Meade, MD
for the SLEAP Investigators and the Canadian Critical Care Trials Group

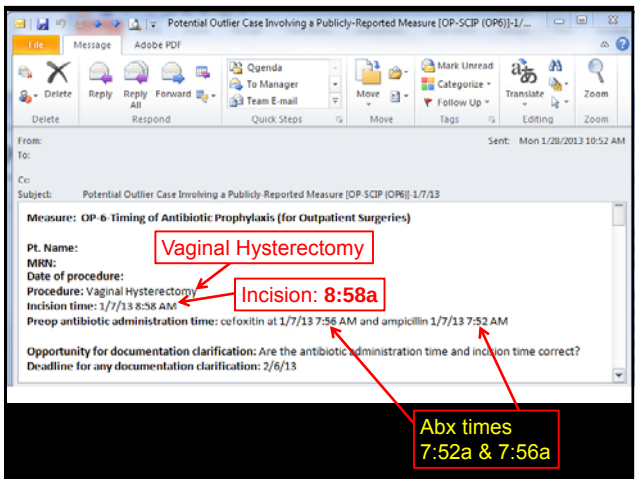
NO difference in ventilator days
NO difference in ICU days
NO difference in delirium
Greater nursing workload with DSI

JAMA 2012;308:1985-92

I am a fan of performance measurement!



(…Despite what I've just been saying for the past 29 minutes…)



What happened?

- We investigated
- The procedure began with insertion of the uterine manipulator
- That part started right after antibiotic administration
- But insertion took almost 1 hr
- So abdominal incision occurred outside the antibiotic window

a. Can we redefine incision to include insertion of the manipulator?
b. When SHOULD we give antibiotics for this procedure?

Multiple lung abscesses secondary to a uterine empyema caused by an intrauterine device

M. van Laren · N. C. van Walree · J. A. J. W. Kluytmans

Infection 2011;39:385-7

Staphylococcal septicaemia after insertion of an intrauterine contraceptive device

SIR,—Your recent leading article on toxic shock and tampons (1 November, p 1161) prompts me to report a case of pelvic infection and staphylococcal septicaemia

Br Med J 1980; 281:1639

Summary

- It's hard to disagree with performance measurement. After all, the alternative is chaos
- But reasonable criticisms can be made of contemporary efforts to measure (and incentivize) performance in medicne
- Among these are efficacy, effects on the underserved, information accuracy, identification of appropriate metrics, and suppression of emerging technologies

Summary II

- Tools to address these criticisms, including risk adjustment, electronic health records, and high quality high volume databases exist, but need refinement
- A more consistent evidence base would also help
- Upsides of performance measurement include development of an infrastructure to “fill in the gaps” in clinical care
- I am a fan!

Program Material

Friday, April 5, 2013

EAB Program (Part 2) Faculty Development

- **Challenges and Solutions to Mentorship in Anesthesiology**
  Monica S. Vavilala, M.D.
- **Faculty Attrition: Is it a Problem?**
  Brenda A. Bucklin, M.D.
- **Burnout or Whining, You Decide**
  Robert R. Gaiser, M.D.

Challenges and Solutions to Mentorship in Anesthesiology

Monica S. Vavilala, M.D.

Mentorship is a critical component of career development in academic medicine. Yet, it is often difficult to define or measure. Moreover, there are few formal mentorship programs in academic anesthesiology. The University of Washington's Faculty Fellowship Program, now in year 3, is one attempt to provide a structured mentorship and career development program aimed at developing academic anesthesiologists of tomorrow.

Introduction

Academic anesthesiology is at a crossroad. For decades, we have successfully trained physicians for high quality operating room anesthesiology care and a much smaller workforce for intensive care and pain medicine. Our specialty has been visionary, leading medicine (often a decade ahead of other specialties) in establishing the fields of intensive care medicine, patient safety, simulation, and effective health care teams. But now, anesthesiology needs to go beyond clinical expertise and provide broader training for new clinical and biomedical paradigms resulting from massive health care reform. Indeed, it is the job of academic anesthesiology departments today to be developing leaders who can thrive in fields as diverse as in tele-medicine, palliative care, efficient patient flow throughout the entire hospital, metrics based care, interdisciplinary perioperative acute pain, management of resources in the high acuity (ICU) hospitals of the future, development of new global health paradigms, and developing the evidence based studies destined to become the perioperative "protocols of the future" for peri-procedure patients. In order to provide this much needed training for upcoming leaders in our specialty, the University of Washington has developed a unique non-ACGME Faculty Fellowship program.

What is the Problem ?

Currently, the ability of academic departments to develop the anesthesiology leaders of tomorrow is constrained by the lack of investment in our workforce, whether it is trainees or faculty. For example, the specialty of anesthesiology represents 6% of the entire medical workforce but is the recipient of a mere 1% of federal funding from the National Institutes of Health. Impending health care changes and concerns about anesthesiologists being marginalized clinically add to the uncertainty regarding the future role of anesthesiologists in health care. Yet, we know the value that anesthesiologists can and do bring to patients and health care. Consequently, there is an unmet need and anesthesiologists must act now to increase stage presence among clinician scientists from other medical specialties and to secure its clinical presence among a dynamically changing and uncertain clinical health care system.

What Can We Do ?

The good news is that academic anesthesiology is uniquely positioned to add value to the health care system by developing tomorrow's perioperative leaders. Developing strategies that transform residents and fellows from providers of anesthesia care to that of anesthesiology experts is feasible at both the resident and fellow levels. At the resident level, programs can create specialized tracks (e.g., Apgar and Bonica scholars) for trainees aspiring to be future researchers. Unfortunately, ACGME fellowships are typically one year in duration and focus on providing clinical subspecialty expertise alone, a process which by itself does not necessarily provide trainees with academic or perioperative efficiency skill sets needed to meet the challenge of producing future thought leaders.

The Faculty Fellowship Program at the University of Washington

Over the last 3 years, we at the University of Washington have developed a new Faculty Fellowship Program that enrolls post graduates either after an anesthesiology residency or after an ACGME fellowship. While a Faculty Fellowship can be one year in duration, many of these trainees choose to complete master's level training that may require more than one year to complete, depending on the nature of the training. The program reports to the Vice Chair for Education for fellow issues and to the Chair for faculty matters. Trainees function as attendings (2 days/week; 10 hour days plus 3 in hospital non-day calls totaling 1415 hours) and as fellows (3 days per week) at a salary that is higher than that of an ACGME fellow and between that of a fellow and attending. This hybrid model is financially self sustaining and allows residency graduates to transition from residency to attending in a supportive environment while having in depth learning in selected areas that are not offered via the ACGME route, without external grant support. Those will external grant funding (e.g. NIH T32, K08, KL2, K99/R00, etc) can reduce their clinical faculty service time to 1 day/week. One of our current ICU Faculty Fellows who came to the University of Washington after completing her a**nesthesiology residency at Northwestern University's Feinberg School of Medicine**, Nita Khandelwal, says "I chose to do a Faculty Fellowship after my ACGME ICU Medicine fellowship because it afforded me the non-clinical time I needed to complete my master's degree in pharmacoeconomics." Such training provides depth in anesthesiology leaders of the future to merge academic outcomes research with health care reform imperatives. Having this next step post residency enhances the ability of many of our graduates to do more academic training in a variety of specialized areas without the fiscal constraints ACGME fellowships impose.

Select examples of post residency Faculty Fellowships that are offered at the University of Washington that combine further subspecialty training and an academic project include neuroanesthesiology, trauma anesthesiology, regional anesthesia obstetric anesthesia, pre-surgery evaluation, or unique combinations of subspecialty expertise such as thoracic/vascular training or pediatric pain or pediatric regional anesthesiology. More often academic training is sought by our graduating residents and fellows. This can range from classic research (laboratory-based, translational, clinical outcomes) to more modern academic specialties pertaining to health care reform such as quality and safety, public policy, education research, and international health from an academic discipline (in addition to practical and experiential. The goal is to provide the tools for changing requirements of the future. Because these Faculty Fellows are spending extra time in training, the department insists that one of their main mentors be nationally funded and recognized in their discipline, and ideally this individual should be a faculty member in another department. We find this provides crucial interdisciplinary training at the highest level, effectively preparing those in anesthesiology to think beyond our specialty in important ways. This year, we have 15 Faculty Fellows; almost half of whom who have already completed a one year clinical fellowship are now pursuing advanced degrees. These degrees include a Master's in Public Health (with options of epidemiology, clinical outcomes, public

health, or genomics tracks), Masters in Public Health in International Health Metrics and Evaluation, Master's of Business Administration (offered through the UW Foster School of Business), and a Master's Degree in Pharmacoeconomics (offered through the UW School of Pharmacy) (http://depts.washington.edu/anesth/education/fellows/index.shtml). Other options for our new graduates include degree programs through the School of Engineering (focused on systems engineering and efficiencies), as well as courses in industrial hygiene and environmental medicine. Non-degree certificate courses are also available. Ian Slade who is currently chief resident in the Department will continue as a Faculty Fellow and says, "I chose this path because it provides the protected non-clinical time and dedicated mentorship needed for an in-depth training experience in the science behind patient safety and quality improvement research."

What distinguishes the Faculty Fellowship program at the University of Washington is an integrated approach to this training, marked by a formal application process with fixed deadline, a department supported program assistant, an program advisory panel, vetted curricula with goals and objectives, identification of a fellowship director, educational activities within each fellowship, availability of monthly journal clubs, completion of an academic patient-oriented, health services or basic project, presentation at the annual departmental spring academic evening, formal evaluation process by fellowship directors (for fellow component) and clinical service chiefs (for faculty component), and quarterly educational seminars (e.g., career development, how to choose a mentor and work in progress sessions) for all Faculty Fellows. Mid-year and end of year surveys that these trainees complete ensures interim and final program feedback to the training program. Program updates and feedback are regularly shared with the Department leadership and department overall so as to integrate its place within the Department functionality. This formal structure has decreased the variability in trainee experience, allows the Department of Anesthesiology & Pain Medicine to provide the trainee with a certificate. Such formality enables future employers and patients to have confidence that the trainee has indeed received state of the art education to be both a content expert and a thought leader by the time of graduation.

Creation of the Faculty Fellowship program in the Department of Anesthesiology has been timely not only based on the needs of the specialty but also because our residents and fellows understand that health care and academic medicine is changing. The Faculty Fellowship program is growing and will ideally become a 2 year training program with half of the class entering each year for a staggered start. Faculty Fellows come from numerous anesthesiology residency and fellowship programs across the U.S. This innovative training program is viewed by our applicants as a way to secure their future. For the discipline of anesthesiology, this may be one way of developing depth and breadth for the specialty and, importantly, make contributions to improvements in health care systems and public health across all of medicine.

Faculty Attrition: Is it a Problem?

Brenda A. Bucklin, M.D.

Notes: _____

Faculty Attrition: Is it a real problem?

Brenda A. Bucklin, M.D.
Professor of Anesthesiology
Assistant Dean, Clinical Core Curriculum
University of Colorado School of Medicine

Challenges of Academic Health Centers

- Better alignment of AHC "product" with health care needs of public
- Sustainable funding model of AHCs
- Adjusting to implications of health care reform
- Resources to keep the "academic" in AHC

Academic Medicine: State of the faculty in the last 50 years…

- Faculty has grown by ~800%.
- Faculty has become more diverse but does not reflect the general population.
- Number of faculty who have been promoted and tenured has declined.
- Financial model for AHCs has changed dramatically.
- Attrition has been stable but there are new concerns.
- Academic medicine remains an attractive career.

Source: 2010 GFA Professional Development Conference

By the numbers…

5 of every 10 clinical faculty members leave their medical school appointments within 10 years, and as many as 4 out of 10 leave academic medicine entirely.

AAMC Analysis in Brief. 2008;8(4)

Lecture Outline

- Academic Medicine: the workforce
- The cost of faculty attrition
- Predictors of attrition
- An approach to faculty attrition

ACADEMIC MEDICINE: WORKFORCE

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Generations in the Workplace

Characteristics	Baby Boomers 1943-60	Generation X 1960-1980	Millennials 1980-2000
Defining events	Prosperity, a TV, Vietnam War, Civil Rights movement, assassinations	Women's rights, PCs, AIDS, latchkey kids, single-parent families	Terrorism, school safety, multiculturalism, internet
Assets	Service-oriented, driven, desire to please, good team player	Adaptable, independent, techno-savvy, unintimidated by authority, creative	Optimistic, heroic spirit, multi-tasker, techno-savvy
Liabilities	Self-centered, judgmental, uncomfortable with conflict	Impatient, poor people skills, cynical	Needs structure and supervision, inexperienced with difficult people
Message that motivates	*"You're important to our success."*	*"Do it your way."*	*"You'll be working with other bright and creative people."*

Generation X: Implications for Faculty Recruitment and Development in Academic Health Centers
Bichel J, Brown AJ.
Acad Med 2005; 80: 205-10.

Boomers (1945-62)

- Work hard out of loyalty
- Expect long-term job
- Pay dues
- Self-sacrifice is a virtue
- Respect authority

Generation X (1963-81)

- Work hard if balance allowed
- Expect many job searches
- Paying dues not relevant
- Occasional self-sacrifice
- Question authority

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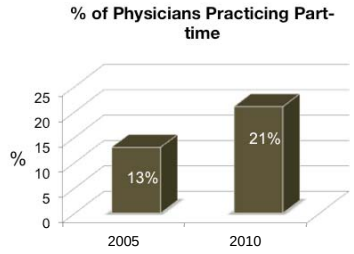
Part-time workforce has grown by 62%



Source: 2010 Cejka Search and AMGA Physician Retention Survey

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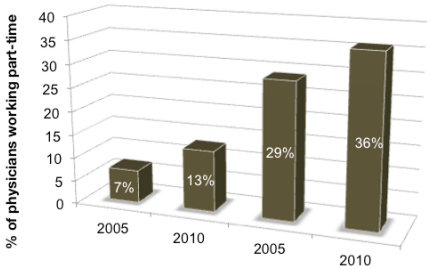
Male and Female Part-time Physician Workforce



Source: 2010 Cejka Search and AMGA Physician Retention Survey

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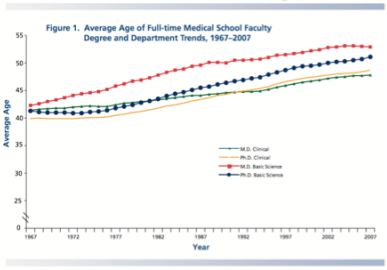
Aging of Full-Time U.S. Medical School Faculty: 1967-2007



AAMC Analysis in Brief. 2009;9(4)

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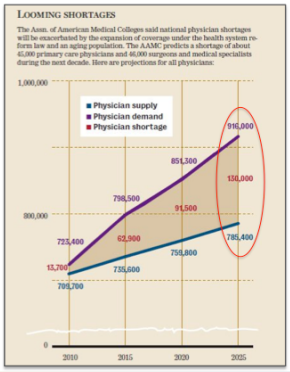


By the end of the decade, there will be a shortage of over 90,000 physicians, "leaving patients with cancer, Alzheimers disease, hip fractures and other ailments without immediate access to necessary care."

AAMC Center for Workforce Studies

Contributing to the shortage…

- 15 million patients become eligible for Medicare
- Support for physician training has been "frozen" since 1997
- 32 million younger Americans become newly insured
- Educating and training physicians takes up to a decade
- Older patients are sicker with multiple chronic conditions

The hidden challenge of physician shortage…

"Academic medical centers need to consider what downstream effects shortages of talent have overall – and in specialties and subspecialties particularly – for their ability to recruit and retain top talent. Given that in today's highly competitive war for talent, academic medical centers vie not only with peer institutions, but also with "private practice, hospitals, industry, and other options that physicians have."

William T. Mallon, Ed.D.
AAMC, Senior Director
Organizational Learning and Research, 2010

THE COST OF FACULTY ATTRITION

Quantifiable Components of Turnover Cost

Hiring + Training = ~2% of annual operating budget

- Hiring
- Training
- Reduced Productivity

Health Care Manage Review. 2004; 29: 2-7

Calculation of replacing faculty who intend to leave their organization

	# of faculty intending to leave	Mean cost of replacing one faculty member	Cost of replacing faculty in AAMC sample
Generalists	72	$115,554	$8,319,888
Subspecialists	271	$286,503	$77,642,313
Surgery specialists	38	$587,123	$22,310,750
Total	381	------	$108,272,951
Average per institution	17	------	$4,707,520

Acad Med 2009; 84:32-36
AAMC Faculty Forward 2010

Economics of New Faculty Hires in Basic Science

University of Rochester School of Medicine and Dentistry

Total Investment: $69 million

Direct Costs: $33.1 million + ***Indirect Costs: $35.9 million***

Faculty, salary, benefits	Facilities
Support for additional personnel	Depreciation
Support for equipment	University-wide indirects

Cohort of 25 newly hired basic science faculty in 3 newly created centers

Total extramural grants: $99.7 million
Direct costs: $70.7 million + Indirect costs $29.1 million

Economics of New Faculty Hires in Basic Science

- Of the 25 faculty members hired between 1999 and 2004, 24 (96%) remained at the school through 2006.
- Faculty generated $1.45 in total grant revenue per dollar invested.
- Start-up expenses and incomplete recovery of indirect costs required the school to add 40 cents to every grant dollar generated to achieve financial equilibrium.

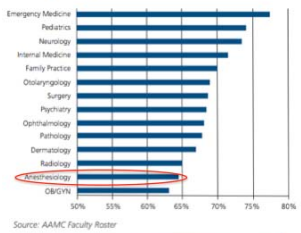
Conclusion: Investments in basic science research, even when successful, may require significant financial subsidies from academic health centers.

Whatever the reasons, faculty attrition represents a serious loss of human and financial capital that may threaten the research, teaching and clinical service missions of institutions.

Acad Med 2009;84:32-36
Health Care Manage Rev 2004;84:26-31
Acad Med 2009;84:26-31

PREDICTORS OF FACULTY ATTRITION

Figure 1. Average Five-year Retention Rates for Clinical M.D. Faculty by Department (1999-2003 Cohorts)



Retention of full-time clinical M.D. faculty at U.S. Medical Schools

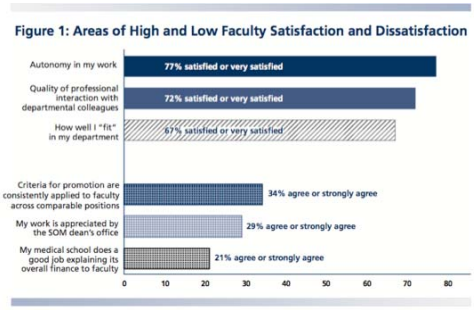
AAMC Analysis in Brief. 2011;11(2)

Clinical Faculty Satisfaction with the Academic Medicine Workplace

	Satisfaction with medical school as a place to work		Satisfaction with department as a place to work		Agreement with choosing an academic career again	
	N (%) satisfied or very satisfied	Dept. Rank	N (%) satisfied or very satisfied	Dept. Rank	N (%) agree or strongly agree	Dept. Rank
Anesthesiology	189 (51)	17	236 (64)	16	258 (77)	17
Dermatology	61 (75)	3	66 (82)	2	61 (81)	14
Internal Medicine	243 (71)	1	239 (70)	11	292 (91)	2
Neurology	145 (68)	5	155 (72)	7	186 (91)	1
Pediatrics	205 (72)	2	228 (81)	4	238 (88)	4
Surgery	59 (51)	16	76 (66)	14	102 (90)	3

AAMC Faculty Forward June 2010

U.S. Medical School Faculty Job Satisfaction



AAMC Analysis in Brief. 2008;8(5)

U.S. Medical School Faculty Job Satisfaction

Areas of Disconnect Between Faculty Values and Workplace Opportunities		
Overall satisfaction	Agreement that: "If I had to do all over, I would again choose an academic career."	78%
	Agreement that: "If I had to do all over, I would again choose to work at this medical school"	65%
Collaboration	Importance of opportunities to collaborate with faculty	75-90%
	Satisfaction with opportunities to collaborate with faculty	44-65%
Feedback	Importance of receiving feedback about performance from unit head	90%
	Usefulness of feedback from unit head about career performance	69%

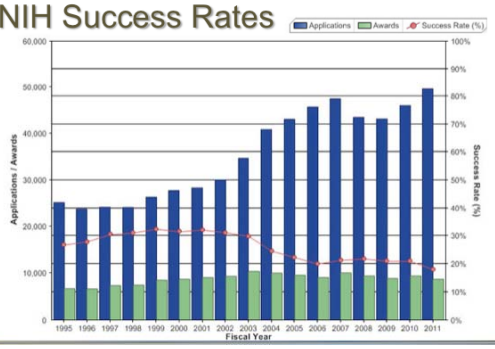
Burnout

- Excessive workload
- Loss of autonomy
- Inefficiency due to excessive administrative burdens
- Decline in sense of meaning that physicians derive from work
- Difficulty integrating personal and professional life

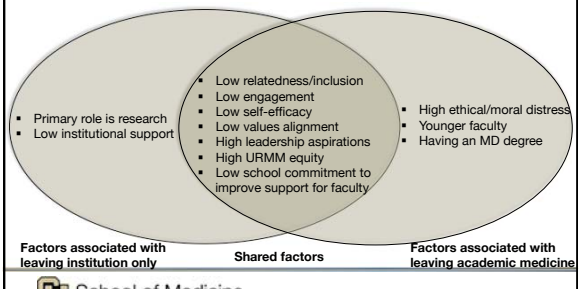
Burnout and satisfaction with work-life balance among U.S. physicians relative to the general U.S. population
Shanafelt TD, Boone S, Tan L et al.
Arch Intern Med; 2012; 172: 1377-1385.

Burnout is more common among physicians than among other US workers. Physicians in specialties at the front line of care access seem to be at greatest risk. Of 27,276 physicians who received an invitation to participate, 7288 (26.7%) completed surveys. When assessed using the Maslach Burnout Inventory, 45.8% of physicians reported at least 1 symptom of burnout.

NIH Success Rates



Why are a quarter of faculty considering leaving academic medicine? A study of their perceptions of institutional culture and intentions to leave at 26 respresentative U.S. medical schools
Pololi LH, Krupat E, Civian JT, et al.
Acad Med; 2012; 87: 1-11.



Medical school faculty discontent: prevalence and predictors of intent to leave academic centers
Lowenstein SR, Fernandez G, Crane LA.
BMC Med Ed; 2007; 7: 37.

Predictors of Serious Intent to Leave

	OR (CI 95)
Difficulties balancing work and family	3.52 (CI 95: 2.34, 5.30)
Absence of faculty development programs	3.03 (CI 95: 2.00, 4.60)
Lack of recognition for clinical work	2.73 (CI 95: 1.60, 4.68)
Lack of recognition for teaching	2.47 (CI 95: 1.59, 3.83)
Absence of academic community	2.67 (CI 95: 1.86, 3.83)
Failure of chairs to evaluate academic progress regularly	2.60 (CI 95: 1.80, 3.74)

236 of 532 (40%) faculty members were seriously considering leaving academic medicine in the next 5 years.

Predictors of Early Faculty Attrition

Strongest Predictors of Resignation in 3 Years	OR
Department Chair does not establish an environment that fosters teaching, research, creativity, and service to School and community	6.03 (1.84, 19.69)
Extensive involvement in clinical care (>50% of time)	3.93 (1.29, 11.93)
Lack of interest in faculty development by Department Chair	3.84 (1.25, 11.81)
Department does not foster a climate of inclusiveness, respect, and open communication	3.21 (1.04, 9.98)
School does not reward excellence in clinical service	3.87 (1.04, 14.41)

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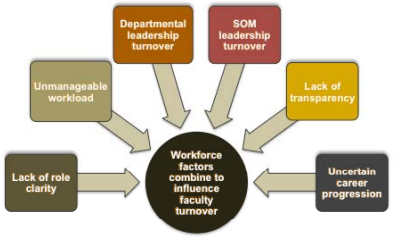
Regrettable Losses: Why do talented faculty leave their institutions?



Faculty Forward Project of the AAMC
Abstract AAMC GFA 2011

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FACULTY ATTRITION: AN APPROACH

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Next-generation Recruits

- Insistent about balancing work schedule with the rest of their lives (e.g., contain work hours, know specifics about call frequency)
- Want mentoring opportunities
- Seek training in leadership skills
- Have an ingrained expectation for collaboration across departmental boundaries

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Multigenerational Challenges in Academic Medicine UCDavis's Responses
Howell LP, Servis G, Bonham A.
Acad Med; 2005; 80: 528-532.

1. Policy changes related to work-life balance
2. Utilize multiple faculty tracks
3. Allow part-time faculty appointments
4. Create a variety of faculty development programs
5. Define appropriate rewards and incentives through compensation plans

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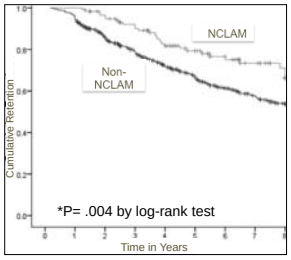
Retention of junior faculty in academic medicine at the University of California, San Diego

Ries A, Wingard D, Morgan C et al.
Acad Med; 2009; 84: 37-41.



After adjusting for hire date, gender, and ethnicity, new asst. professors in the faculty development program were 67% more likely to remain at UCSD compared to non-participating faculty members.

Lessons from the Corporate World

- ✓ Recognize dependence of financial future on recruitment and retention of diverse and talented staff
- ✓ Limit the costs of lost opportunities and reduced productivity
- ✓ Build a diverse portfolio of talent
- ✓ Invest strategically and protect investments over time

Conclusions

- Some attrition is inevitable and likely beneficial.
- Attrition is an opportunity for recruitment of new faculty with novel and innovative ideas.
- Institutions and departments should regularly access rates of attrition and its cost.
- It will be important to align expectations and determine how to best recruit, integrate, and support multigenerational faculty members in their new roles.

Burnout or Whining, You Decide

Robert R. Gaiser, M.D.

Notes: _____

Burnout or Whining, YOU Decide

ROBERT GAISER, M.D., M.S.ED.
PROFESSOR OF ANESTHESIOLOGY AND CRITICAL CARE
HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

No financial conflicts and No off-label use

Goals

- Review the concept of burnout
- Identify factors that cause burnout
- Decide whether burnout is a result of an individual or a system
- Identify means to prevent burnout

History of Anesthesiologists 1947-1966

- Examined incidence of deaths among anesthesiologists
- 441 deaths identified
- Compared to U.S. males and men policyholders of Metropolitan Life Insurance

- Death from Suicide

2X General Population

Esp Age < 45 yrs

Bruce DL. Anesthesiology 1968;29:565

History of Anesthesiologists 1979-1995

- Physician Master File database to identify anesthesiologists and general internists
- 2458 deaths of anesthesiologists; 2376 deaths of internists

- No difference in risk of death from cancer or heart disease

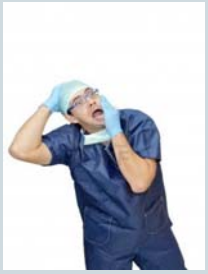
Death from Suicide RR 1.45

Drug Related Death RR 2.79

Alexander BH. Anesthesiology 2000;93:922

Anesthesiologists are STRESSED!

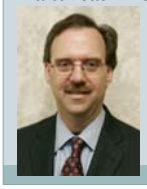
- Time constraints
- Excessive (physical and mental) workload
- Complexity of the task
- Responsibility and fear of harming patients
- Workplace atmosphere
- Lack of job control
- Combining family with being on call



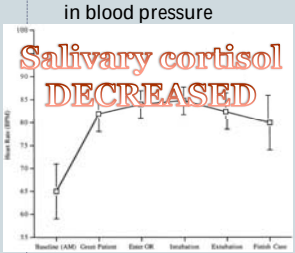
Nyssen AS. Curr Opin Anaesthesiol 2008;21:406

Is it REALLY Doing Anesthesia?

- 38 anesthesiologists anesthetizing 208 patients were studied
- HR, BP, Anxiety levels, salivary cortisol assessed after each induction



- Non-significant changes in blood pressure



Kain ZN. Anesth Analg 2002;95:177

SO IF IT ISN'T DOING ANESTHESIA

WHAT IS IT?

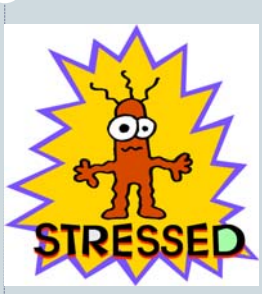
Operating Room Noise

- 20 major surgical instruments from 5 specialties
- Routinely used instruments – 131 dB
- Exceed OSHA and NIOSH recommendations

Fritsch MH. Otology & Neurotology 2010;31:715

On-Call

- Heart rate variability measured during and post-call in 19 anesthesiologists and 16 pediatricians/ENT surgeons
- No difference in day or post call
- During call, high frequency lower high frequency during call for anesthesiologists
  - Decreased parasympathetic activity



Malmberg B. Int Archives Occupation Enviorn Health 2011;84:293

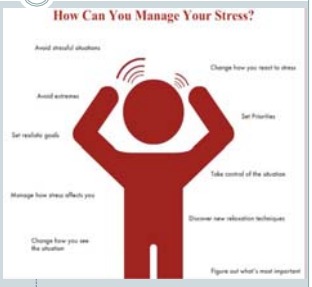
On Call

- Measured plasma TSH and cortisol measured day of call and 1 to 3 days postcall for 19 anesthesiologists and 18 pediatricians/ENT surgeons
- TSH decreased post-call in both groups
  - Stressed induced inhibition on hypothalamic level
- Cortisol rise day of call for P/ENT

Malmberg B. Acta Anaesth Scand 2007;51:823

Stress

- Some stress is good
  - Increases concentration
  - Helps to achieve optimal performance
- Some stress is bad
  - Higher incidence of suicide
  - Higher incidence of chemical dependence
  - Burnout



Jackson SH. Acta Anaesthesiol Scand 1999;43:583

Burnout

- A fire that is deliberately set inside a control line for the purposes of consuming fuel between the edge of a wildfire and the control line

Implications of Burnout

- Somebody was "burning" before
- Fires can not burn endlessly
- Does not occur overnight

Burnout

- First described by Freudenberger, a psychoanalyst
- Seeing patients all day in the free clinic and then his practice at night
- "to fail, wear out, or become exhausted by making excessive demand on energy, strength, or resources"
- "A human must be able to balance, in the helping situation, between the self and others in order to avoid becoming burned out"

Cult Med Psychiatry 2009;33:538

Burn Out

- Three Key Aspects
  - Increased feelings of emotional exhaustion
  - Depersonalization – the development of negative cynical attitudes and feelings about the client
  - Lack of personal accomplishment

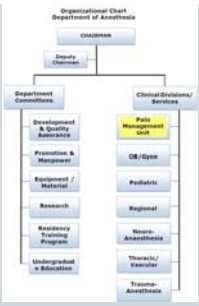
Maslach C. Ann Rev Psychol 2001;52:397

Burn Out is a Medical Diagnosis

- ICD-10
- Diagnosis code: Z73.0
- Criteria:
  - Persistent and distressing complaints of exhaustion
  - Unable to recover from symptoms by rest
  - Duration: 3 months
  - Two of the following six: muscular aches, dizziness, tension headaches, sleep disturbance, inability to relax, irritability

What leads to Burnout?

- Excessive workload
- Time Pressure
- Lack of resources
- Organizational context
- Demanding family environment



Nyssen AS. Curr Opin Anaesthesiol 2008;21:406

Risk Factors for Burnout

- Personality Characteristics
  - Low self-esteem
  - Higher vulnerability
  - Competitiveness
  - Excessive need for control
- Job Attitudes
  - Higher job expectations
  - Perceive work as challenging

Lederer W. Acta Anaesthesiol Scand 2006;50:58


Scoring the abbreviated Maslach Burnout Inventory

Burnout and Perioperative Personnel

- Maslach Burnout Inventory to perioperative personnel
- 145 responses (22.8% residents, 23.4% attendings, 43.4% nurses, 10.3% other personnel)
- Physicians higher risk of burnout
- Anesthesiologists have higher risk than surgeon
- Residents have the highest risk
  - Scored highest overall
  - Emotional exhaustion
  - Depersonalization
    - One SD different

Hyman SA. Anesthesiology 2011;114:194

Burnout and Anesthesiologists

- 89 anesthesiol… observed and … questionnaire
  - Assessment of… conditions
  - Assessment of… health and str…

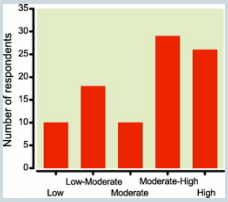
…ologists NOT …or burnout
- …f working …s
- …ntrol of time
- …able to …icate

…ologists AT …urnout
- …sical complaints
- …ob dissatisfaction
- …d ability to …solve

Lederer W. Acta Anaesthiol Scand 2006;50:58

Chairperson and Burnout

- Survey to 117 Chairs (102 responded – nine were incomplete)
- Of the 93 Chairs
  - 32 high satisfaction
  - 26 likely to step down
  - 26 met criteria for high burnout
  - 29 met criteria for extremely high burnout
  - Predictors
    - Current job satisfaction
    - Spousal/significant other support



De Oliveira GS. Anesthesiology 2011;114:181

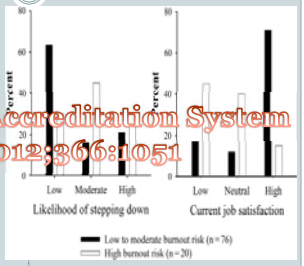
Chairpersons and Burnout

- 69% high emotional exhaustion
- 60% high depersonalization
- 39% low personal accomplishment

De Oliveira GS. Anesthesiology 2011;114:181

Program Director and Burnout

- 100 program directors responded to survey (76%)
- 20% met criteria for high burnout risk
- 22% reported stepping down in 2 years
- Report low job satisfaction
  - Compliance issues
  - Self-assessment of effectiveness
  - Family support
  - Impact of stressful factors



De Oliveira GS Jr. J Clin Anesth 2011;23:1176

Avoiding Burnout

- 7197 surgeons responded to survey from American College of Surgery
- Surgeons that did not have burnout
  - Find meaning in work
  - Focus on what is important in life
  - Maintain a positive outlook
  - Work/life balance

Shanafelt TD. Annals Surgery 2012;255:625

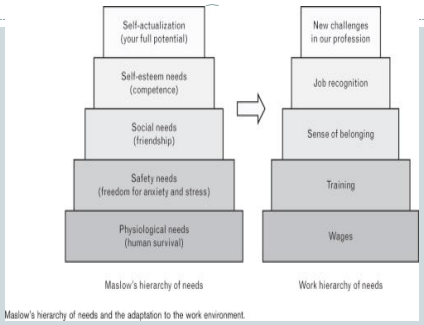
Preventing Burnout

- Internal Resources
  - Active coping strategies
  - Positive self-evaluation
  - Rational attitude
  - Involvement
  - Intrinsic motivation
- External Resources
  - Social support
  - Gain control of work
  - Participate in decision making
  - Time management

Burnout ⟷ Career Satisfaction

Perception is Reality

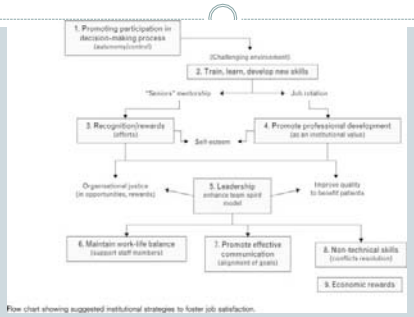
Job Satisfaction



Maslow's hierarchy of needs and the adaptation to the work environment.

Rama-Maceiras P. Eur J Anaesthesiol 2012;29:311

Job Satisfaction



Flow chart showing suggested institutional strategies to foster job satisfaction.

Rama-Maceiras P. Eur J Anaesthesiol 2012;29:311

Burnout

- What is burnout?

ith

Program Material

Friday, April 5, 2013

SAB Plenary Lecture: Anesthetics - The Final Frontier
Beverley A. Orser, M.D., Ph.D.

SAB Plenary Lecture: Anesthetics - The Final Frontier

Beverley A. Orser, M.D., Ph.D.

Does memory loss during anesthesia come at a cost? I will present clinical and animal studies that offer insights into the cause of memory loss during anesthesia as well as undesirable memory deficits that persist long after the drugs have been eliminated.

Program Material

Friday, April 5, 2013

Anesthesiology Foundation Funding Opportunities

FAER Funding
Denham Ward, M.D., Ph.D.

IARS Funding
Alex S. Evers, M.D.

SCA Funding
Joyce A. Wahr, M.D.

APSF Funding
Steven K. Howard, M.D.

Anesthesiology Foundation Funding Opportunities: FAER Funding

Denham Ward, M.D., Ph.D.

- Mentored Research Training Grant – Clinical or Translational
- Mentored Research Training Grant – Basic Science
- Mentored Research Training Grant – Healthcare Services Research
- Research Fellowship Grant
- Research in Education Grant

Rising to New Heights on the Path to Discovery
Since its founding in 1986, the Foundation for Anesthesia Education and Research has provided research grants and educational opportunities to anesthesiologists to prepare them for careers in academic anesthesiology and to become independent investigators.

FAER's current research grant opportunities include the following.

Research Fellowship Grant
The Research Fellowship Grant is a one-year, $75,000 grant for anesthesiology residents after the CA-1 year. The RFG is awarded in conjunction with clinical training in an anesthesiology residency or fellowship program. The RFG requires 80 percent research time.

Mentored Research Training Grant — Basic Science
The Mentored Research Training Grant – Basic Science is a two-year, $175,000 grant for anesthesiology faculty members who have completed their residencies or fellowships within the past 10 years. The MRTG-BS requires 75 percent research time.

Mentored Research Training Grant — Clinical or Translational
The Mentored Research Training Grant – Clinical or Translational is a two-year, $175,000 grant for anesthesiology faculty members who have completed their residencies or fellowships within the past 10 years. The MRTG-CT requires 75 percent research time.

Mentored Research Training Grant — Health Services Research
The Mentored Research Training Grant – Healthcare Services Research, a pilot program in 2013, is a two-year, $175,000 grant for anesthesiology faculty members who have completed their residencies within the past 10 years. The MRTG-HSR requires 75 percent research time.

Research in Education Grant
The Research in Education Grant is a two-year, $100,000 grant available for faculty members of all ranks. Year one and year two are funded up to $50,000. The REG is focused on developing innovative techniques for anesthesia education. The REG requires 40 percent research time.

Additional Information
- FAER has one grant funding cycle per year.
- The deadline for FAER grant applications is February 15.
- For more information about FAER research grants, visit FAER.org/research-grants.

Notes: _____

Anesthesiology Foundation Funding Opportunities: IARS Funding

Alex S. Evers, M.D.

- IARS Mentored Research Awards (IMRA)
- Frontiers in Anesthesia Research Award (FARA)
- Teaching Recognition Awards (TRA)

Summary

1. What is the IARS?
2. IARS Mission and Goals
3. IARS Research Funding History
4. IARS Research Funding Mechanisms
5. IARS Grant Selection Process

Notes: _____

Anesthesiology Foundation Funding Opportunities: SCA Funding

Joyce A. Wahr, M.D.

- SCA In-Training Grant
- SCA/IARS Starter Grant
- SCA/IARS Mid-Career Grant

Notes: _____

Anesthesiology Foundation Funding Opportunities: APSF Funding

Steven K. Howard, M.D.

The ***Anesthesia Patient Safety Foundation (APSF) Grant Program*** supports research directed towards enhancing anesthesia patient safety. Its major objective is to stimulate and fund studies that will clearly improve patient safety and lead to prevention of mortality and morbidity resulting from anesthesia mishaps. This supports the Mission Statement of the APSF.

PRIORITIES

APSF accepts applications in one of two general categories of identified need: CLINICAL RESEARCH and EDUCATION AND TRAINING. For the 2014 funding cycle the APSF is placing a specific emphasis on: PATIENT SAFETY EDUCATION and MEDICATION & DEVICE SAFETY.

Maximum award: $150,000 for studies conducted over maximum of 2 years (including up to 15% institutional overhead)

Up to six awards per funding cycle

- Anticipated named awards for 2013-14:
  - APSF/ASA President's Endowed Research Award
  - Ellison C. Pierce, Jr., MD Merit Award – $5,000 unrestricted

Grant deadline – online submission: June (06/16/2013)

Range per year of grants submitted: 20-50

- Primary review – during Summer
- Based on primary review – discuss ~ 10 proposals at ASA meeting

Awardees notified: October (during ASA)

Funding start: January 2014

Online Submission: http://apsf.org/grants_guidelines.php

Notes: _____

Program Material

Saturday, April 6, 2013

Host Program

Where We Live?

- **Our Climate**
  Roni Avissar, Ph.D.
- **Our Buildings**
  Elizabeth Plater-Zyberk
- **Our Neighbors**
  Andy S. Gomez, Ph.D.

What We Do?

- **Physics of Collective Behavior**
  Neal Johnson, M.D.
- **Aging and Spirituality**
  Stephen Sapp, Ph.D.
- **Genomics of Alzheimer's**
  Margaret A. Pericak-Vance, Ph.D.

Host Program: Where We Live?

Our Climate

Roni Avissar, Ph.D.

Notes: _____

Host Program: Where We Live?

Our Buildings

Elizabeth Plater-Zyberk

Notes: _____

Host Program: Where We Live?

Our Neighbors

Andy S. Gomez, Ph.D.

We will take a close look at the transformation on South Florida since the 1960's up to now. We will analyze the political, social and economic changes that has developed South Florida as the "Capital of Latin America" and a World Class City besides being one of the major tourist destination in the world.

Host Program: What We Do?
Physics of Collective Behavior

Neal Johnson, M.D.

Everybody knows that life is complicated. However at a deeper level, life is also fundamentally complex which means that it behaves dynamically in a way that is strictly greater than the sum of its parts [1-4]. The idea that the natural phenomena that we observe, including ourselves, cannot be properly understood by simply putting together sets of elementary building blocks, underlies both the fascination and difficulty with providing quantitatively predictive mathematical models of real-world systems across the life sciences. Recently there has been an explosion of interest in the topic of complexity, including complex networks. In this talk, we take a journey through the world of nonlinear systems, chaos, fractals and networks to see how complexity emerges in real-world systems. In particular, we look at the implications of complexity in terms of the likelihood that the system will produce unexpected extremes in behavior – so-called black swans or dragon kings. Examples are discussed in the field of medicine, from the seemingly mundane problem of scheduling surgeries and the real-time management of finite resources, through to the remarkable proposition that human consciousness is related to the complexity which emerges at the physicists' favorite frontier – the crossover between classical and quantum worlds.

References

1. Neil F. Johnson. Simply Complexity. Oneworld Publications, 2009.
2. Steven H. Strogatz. Sync: How Order Emerges From Chaos In the Universe, Nature, and Daily Life. Hyperion, 2004.
3. Ricard Sole and Brian Goodwin. Signs of Life: How Complexity Pervades Biology. Basic Book, 2002.
4. Duncan J. Watts. Six Degrees: The Science of a Connected Age. Norton & Company, 2004.

Host Program: What We Do?
Aging and Spirituality

Stephen Sapp, Ph.D.

Is Aging an Illness or a Psychospiritual Necessity?
Some Suggestions for Moving Beyond the "Medical Model"

In the United States, aging is typically approached as a problem that is (ultimately) amenable to solution by medical/technological means if we but devote enough resources to a solution. This presentation suggests that on the contrary aging is a natural process that must be accepted if we are to get on with the business of dealing with the reality that we *will* inevitably get old (if we live long enough!) and will die. Scientific medicine certainly plays an important role in improving the quality of life as we age; many authorities on aging assert, however, that spiritual issues become increasingly important as human beings age. Indeed, some argue that the older a person gets, the less contemporary *scientific* medicine has to offer. Thus both elders and those providing them with care and services of various kinds need to pay more attention to the task that both the wisdom of the ages and modern thinkers such as Jung, Erikson, Frankl, and Butler have suggested are essential for successful completion of the life cycle, namely, finding *meaning* in having lived and having to die. And this is precisely where religion and spirituality come to the fore.

In the final analysis, then, the real task of aging is a spiritual one, and if health care professionals are to give their patients the best care possible, they must recognize the religious/spiritual concerns that those patients have, especially in situations of vulnerability such as serious illness and approaching death, either from illness or age.

Host Program: What We Do?

Genomics of Alzheimer's

Margaret A. Pericak-Vance, Ph.D.

Notes: _____

Program Material

Saturday, April 6, 2013

SAB Program Introduction
Charles W. Emala, M.D.

SAB Oral Session (Part 2)

Junior Faculty Presentation (Junior Faculty Award)

Optogenetic Stimulation of Dopamine Neurons in the Ventral Tegmental Area
Norman E. Taylor, M.D., Ph.D.[1]; Christa J. Van Dort, Ph.D.[1]; Jonathan Kenny, B.S.[1]; Emery N. Brown, M.D., Ph.D.[1,2]; Ken Solt, M.D.[1]

Resident Presentation (Resident Travel Award)

Novel Chloride Channel Blockers Relax Airway Smooth Muscle: Potential New Tools to Treat Bronchospasm
Jennifer Danielsson, M.D.[1]; Alison Rinderspacher, Ph.D.[2]; Wen Fu, Ph.D.[2]; Yi Zhang, M.D.[2]; Donald W. Landry, M.D., Ph.D.[2]; Charles W. Emala, M.D.[2]

Oral Presentations

General Anesthesia Causes Disturbances of Mitochondrial Morphogenesis and Synaptic Transmission in Developing Rat Brain
Nadia Lunardi, M.D, Ph.D. [1,2]; Victoria Sanchez, B.S.[1,3]; Annalisa Boscolo, M.D.[4]; Pavle Joksovic, M.D.[5]; Slobodan Todorovic, M.D., Ph.D.[1,3]; Vesna Jevtovic-Todorovic, M.D., Ph.D., M.B.A.[1,3]

Modeling the Ischemic Penumbra in C. Elegans
C. Michael Crowder, M.D., Ph.D.; Chun-Ling Sun, Ph.D.; Euysoo Kim, Ph.D.

Zero Tolerance for Chronic Pain
Howard B. Gutstein, M.D.; Katherine Barker, Ph.D.; Shanping Shi, B.S.; Miguel Diaz, B.S.; Bing Mo, Ph.D.;

Critical Role of Interleukin-11 in Isoflurane-Mediated Protection Against Ischemic Acute Kidney Injury
H.T. Lee, M.D., Ph.D.; Mihwa Kim, Pharm.D.; Ahrom Ham, Ph.D.; Joo Yun Kim, Ph.D.

MicroRNAs and Anesthetic Cardioprotection in Diabetes
Zeljko J. Bosnjak, Ph.D.; Jessica Olson, M.S.; Alison Kriegel, Ph.D.; Xiaowen Bai, M.D., Ph.D.; Mingyu Liang, M.B., Ph.D.

Percutaneous Fiber Optic Monitoring for Spinal Cord Ischemia
Angela D'Souza, M.S., BME[1]; Rickson Mesquita, Ph.D.[2]; Thomas V. Bilfinger, M.D.[1]; Robert M. Galler, D.O.[1]; Arjun Yodh, Ph.D.[2]; Thomas F. Floyd, M.D.[1]

Junior Faculty Award

Optogenetic Stimulation of Dopamine Neurons in the Ventral Tegmental Area

Norman E. Taylor, M.D., Ph.D.[1]; Christa J. Van Dort, Ph.D.[1]; Jonathan Kenny, B.S.[1]; Emery N. Brown, M.D., Ph.D.[1,2]; Ken Solt, M.D.[1]
Massachusetts General Hospital[1]; Massachusetts Institute of Technology[2]

Background: Emergence from general anesthesia is clinically viewed as a passive process dictated by drug clearance. Recent studies demonstrated that methylphenidate (a dopamine reuptake inhibitor) and Chloro-APB (a D1 dopamine receptor agonist) actively induce conscious behaviors in anesthetized rats [1,2], a process that we term "reanimation." Although dopamine promotes behavioral arousal, the specific dopaminergic neurons that induce it are unknown. The ventral tegmental area (VTA) and substantia nigra (SN) are the two main dopaminergic nuclei in the brain. We recently found that electrical stimulation of the VTA induces reanimation from isoflurane anesthesia, while stimulation of the SN does not [3], suggesting that dopamine release by VTA neurons causes reanimation. However, electrical stimulation does not specifically target dopamine neurons. Optogenetic tools are now available that allow activation of specific neuronal cell types with pulses of light. The current study was performed to test the hypothesis that selective activation of dopamine neurons in the VTA induces reanimation from general anesthesia.

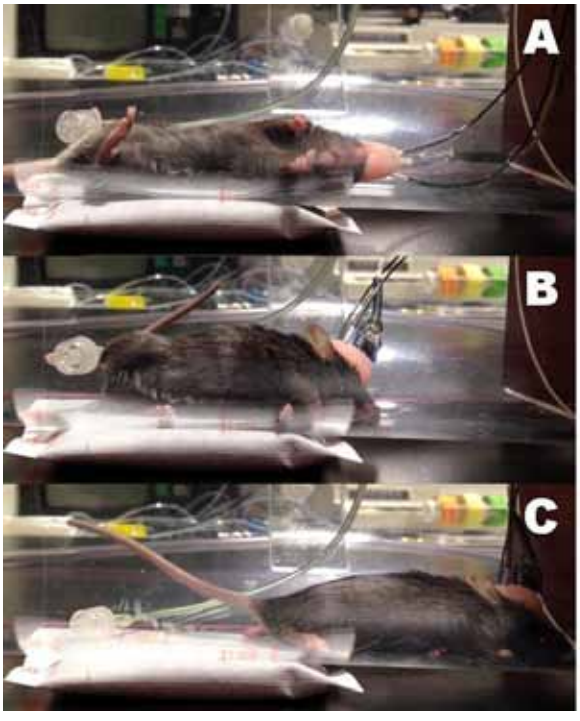
Methods: Genetically modified mice expressing Cre recombinase under the transcriptional control of the dopamine transporter promoter (DAT-cre mice) were used to target dopamine neurons. Anesthetized male DAT-Cre mice were injected with adeno-associated virus carrying FLEX-Channelrhodopsin2 into the VTA or SN, and bilateral fiber-optic cannulas were implanted along with extradural EEG electrodes. The virus causes the expression of Channelrhodopsin2, a light-sensitive ion channel, only in cells that express Cre recombinase. This allows for selective activation of dopamine neurons with pulses of light delivered via the fiberoptic cannulas. After a minimum recovery period of 3 weeks to allow for maximal viral expression, general anesthesia was induced with isoflurane and a dose sufficient to maintain loss of righting with no spontaneous movement was established. During continuous isoflurane anesthesia, optical stimulation of dopamine neurons was initiated using light pulses (480nm, 30mW, 5ms pulses @ 50Hz, 60s on/30s off). After all experiments were completed, histological analysis was performed to confirm the location of the fiber-optic cannulas.

Results: In mice with confirmed fiber-optic cannula placement in the VTA (n=2), light pulses induced arousal and restored the righting reflex during isoflurane anesthesia. Optical stimulation of the VTA also induced a shift in EEG peak power from delta (<4 Hz) to theta (4-8 Hz), indicating arousal. Between stimulation periods, EEG peak power drifted back to delta, and the arousal response waned. In a mouse with the fiber-optic cannula in the SN (n=1), optical stimulation failed to elicit an arousal response during isoflurane anesthesia, and did not induce significant EEG changes.

Conclusions: Dopamine release by VTA neurons induces reanimation from general anesthesia. VTA dopamine neurons represent a novel target to hasten recovery from general anesthesia, and possibly treat emergence-related problems such as cognitive dysfunction.

References:

[1] Solt K, et al. Anesthesiology 2011;115(4):791-803
[2] Taylor NE, et al. Anesthesiology 2013;118(1):30-39
[3] Solt, K, et al. Anesthesiology 2012;117:A543



A. A DAT-CRE mouse under general anesthesia with isoflurane at a dose sufficient to produce loss of righting. The mouse has bilateral fiberoptic cannula aimed at the VTA, where an adeno-associated virus (AAV) vector carrying FLEX-Channelrhodopsin2 was injected and allowed to express for 3 weeks prior to the experiment.

B. Despite continuous general anesthesia with isoflurane, optical stimulation of the VTA with blue light prompted a profound arousal response.

C. Within 10s the mouse has regained the righting reflex, ***while still inhaling isoflurane at the same dose.***

Resident Travel Award

Novel Chloride Channel Blockers Relax Airway Smooth Muscle: Potential New Tools to Treat Bronchospasm

Jennifer Danielsson, M.D.[1]; Alison Rinderspacher, Ph.D.[2]; Wen Fu, Ph.D.[2]; Yi Zhang, M.D.[2]; Donald W. Landry, M.D., Ph.D.[2]; Charles W. Emala, M.D.[2]
Columbia University Medical Center[1]; Columbia University[2]

Introduction: Perioperative bronchospasm refractory to -agonists continues to challenge anesthesiologists and intensivists. We questioned whether chloride channels/transporters are novel targets in the treatment and prevention of bronchospasm. Calcium activated chloride channels (CaCCs) and the sodium potassium chloride cotransporter (NKCC) are 2 potential targets on airway smooth muscle that control cellular chloride flux. In previous studies, combined blockade of CaCCs and NKCC with non-selective CaCC antagonists relaxed acetylcholine induced contractions. We have screened a library of novel compounds, derivatives of anthranilic and indanyloxyacetic acid, that were previously developed as chloride channel antagonists in the kidney. We hypothesized that members of this library would be more potent and/or specific than known CaCC blockers, and that further analysis of the structural and mechanistic differences could aid in novel bronchodilator drug development.

Methods and Results: All studies received IACUC or IRB approval. Closed guinea pig tracheal rings were suspended at 1g tension in oxygenated buffer at 37°C. The library was initially screened by the compounds' ability to relax contractions induced by potassium channel blockade with tetraethylammonium chloride (TEA). 4 of the 20 compounds screened were found to relax a TEA induced contraction. Compounds 1 and 13 were further studied for their potential to relax the maintenance phase of contractions induced by the natural endogenous bronchoconstrictor, acetylcholine (Ach). Treatment with 100uM compound 1 or 13 alone each significantly relaxed contraction (42.9 +/- 4.24% and 65.12 +/- 4.96% of initial Ach muscle force, respectively), while in combination with the NKCC inhibitor, bumetanide (10uM) they relaxed an Ach contraction to an even greater extent (26.54% +/- 2.94% and 28.99% +/- 6.66% of initial Ach muscle force, respectively). Additionally, pretreatment with either compound in combination with bumetanide prior to an acetylcholine challenge attenuated a subsequent contraction.

Human airway smooth muscle from lung transplants were suspended and contracted with Ach. Treatment with 100uM of compounds 1 or 13 relaxed an Ach induced contraction (23.7 +/- 7.8% and 37.4 +/- 5.9% of initial Ach muscle force, respectively). For cellular assays, human airway smooth muscle cells were cultured. Compounds 1 and 13 hyperpolarized the plasma cell membrane (which favors relaxation) as measured by the FLIPR potentiometric fluorescent indicator (143% and 55% decrease in fluorescence compared to vehicle, respectively, n=5). In whole cell patch clamp recordings, compound 13 blocked spontaneous transient inward chloride currents (n=2).

Conclusions: We have identified two novel chloride channel blockers which relax either an established TEA or Ach contraction. Additionally pretreatment attenuated an Ach contraction, and caused a hyperpolarization of plasma membrane potential and an inhibition of chloride current in human airway smooth muscle cells. These functional and electrophysiologic data suggest that modulating airway smooth muscle chloride flux is a novel therapeutic target in asthma and other bronchoconstrictive diseases.

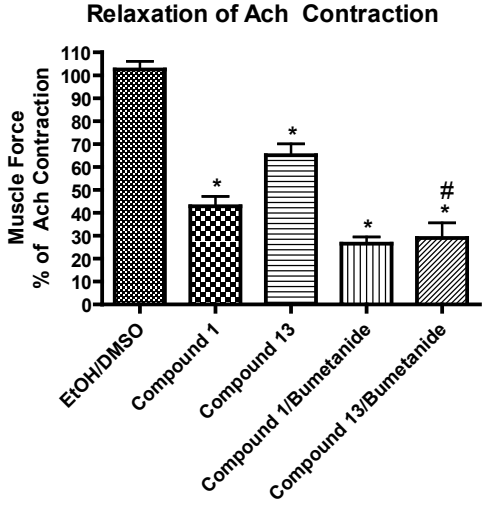


Figure 1. Chloride channel/transporter blockade of an established achetylcholine (Ach) concentration in guinea pig airway smooth muscle. The relaxation induced by the novel chloride channel blockers (100uM compound 1 and 13) was further potentiated by co-blockade of the NKCC by 10uM bumetanide. * p<0.01 compound to respective vehicle control # p<0.01 compound 13 to compound 13/bumetanide, n=5

Oral Presentations

General Anesthesia Causes Disturbances of Mitochondrial Morphogenesis and Synaptic Transmission in Developing Rat Brain

Nadia Lunardi, M.D, Ph.D. [1,2]; Victoria Sanchez, B.S.[1,3]; Annalisa Boscolo, M.D.[4]; Pavle Joksovic, M.D.[5]; Slobodan Todorovic, M.D., Ph.D.[1,3]; Vesna Jevtovic-Todorovic, M.D., Ph.D., M.B.A.[1,3]
Department of Anesthesiology[1], University of Virginia Health System[2], Neuroscience Graduate Program[3], University of Virginia, Charlottesville, Virginia; Department of Anesthesiology and Pathology, University of Padova, Padova, Italy[4]; Department of Psychiatry, Yale University, New Haven, Connecticut[5]

Background: General anesthetics cause neurodegeneration in the developing brain via mitochondria-dependent apoptotic cascade. (1) Exposure to anesthesia at the peak of synaptogenesis causes a significant decrease in the number of synapses in rat subiculum. (2) Synaptogenesis relies on proper mitochondrial function and morphogenesis which suggests that mitochondria could be an important target for anesthesia-induced impairment of synaptic function and neuronal development.

Methods: Rats were exposed to midazolam, nitrous oxide and isoflurane for 6-hours on postnatal day (PND 7). The long-term effects of this anesthesia cocktail synaptic transmission and on the morphology and subcellular distribution of mitochondria were examined in subiculum two weeks after the exposure (PND 21).

Results: Upon ultrastructural examination we noted that the experimental mitochondria underwent two stages of degeneration. An early stage was marked by a dilation of cristae and swelling which gave them enlarged appearance compared to controls. In the late stage, mitochondria appeared dark and condensed. The morphometric analysis of the soma of pyramidal neurons revealed that the experimental mitochondria occupied twice as much cytoplasmic area as the controls (22.5 ± 3.1% vs 13.4 ± 1.2%, P<0.05). Large mitochondria (0.26-0.65 μm2) constituted only 5% of total mitochondria in control animals, whereas more than 15% of the experimental mitochondria were in the large category. The morphometric analysis of the presynaptic neuronal profiles revealed that the experimental mitochondria were on average 38% larger than control ones (P<0.05), resulting in a decreased density of mitochondrial profiles in the proximity of newly developing synapse (P<0.05) where their presence is strategically most important. Electrophysiology studies revealed a 49% decrease in net charge transfer of inhibitory postsynaptic currents (P<0.05), a decreased decay time constant from 58 ± 9 ms to 34 ± 4 ms (P<0.05) and a significantly altered paired pulse ratio (P2/P1) from 0.81 ± 0.02 to 0.87 ± 0.01 (P<0.05) in the experimental animals.(3) These functional findings suggest that both postsynaptic and presynaptic mechanisms contributed to decreased synaptic strength of the inhibitory transmission in the experimental group.

Conclusions: Early exposure to general anesthetics causes long-term impairment of mitochondrial morphogenesis and functional integrity leading to the impairment of synaptic transmission in the developing rat brain. Mitochondria appear to be an important intracellular target in anesthesia-induced developmental neurodegeneration.

1. Jevtovic-Todorovic V et al. J Neurosci 2003; 23:876-82.
2. Lunardi N et al. Neurotox Res 2010; 17:179-88.
3. Sanchez V et al. Anesthesiology 2011; 115:992-1002.

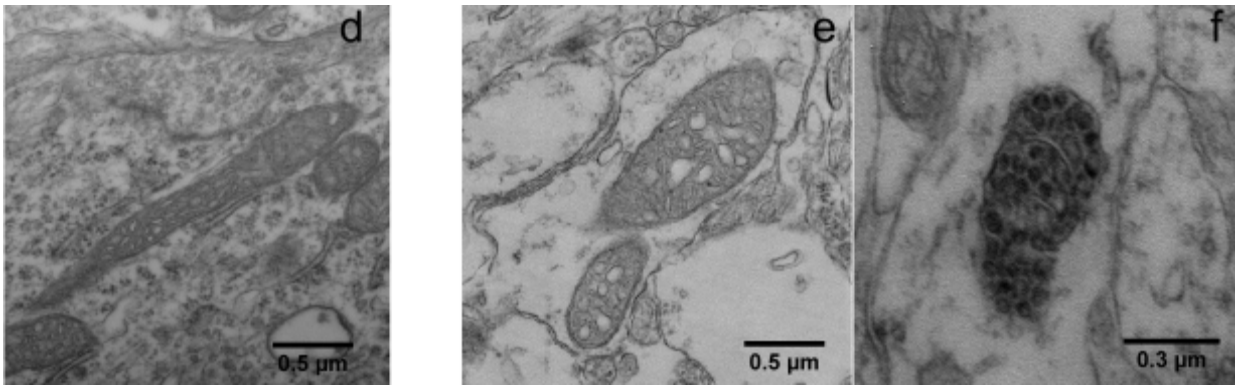


Figure 1: Ultrastructural changes indicative of mitochondria degeneration. Panel d shows a control subiculum. Panels e and f show experimental subiculum. Panel e: mitochondria appeared swollen, with balloon-like cristae, but normal-looking inner and outer membranes (early stage of degeneration). Panel f: dark, condensed and shrunken mitochondrial profiles having no clear outline between the inner and outer membrane (late stage of degeneration).

Oral Presentations

Modeling the Ischemic Penumbra in C. Elegans

C. Michael Crowder, M.D., Ph.D.; Chun-Ling Sun, Ph.D.; Euysoo Kim, Ph.D.
Washington University School of Medicine

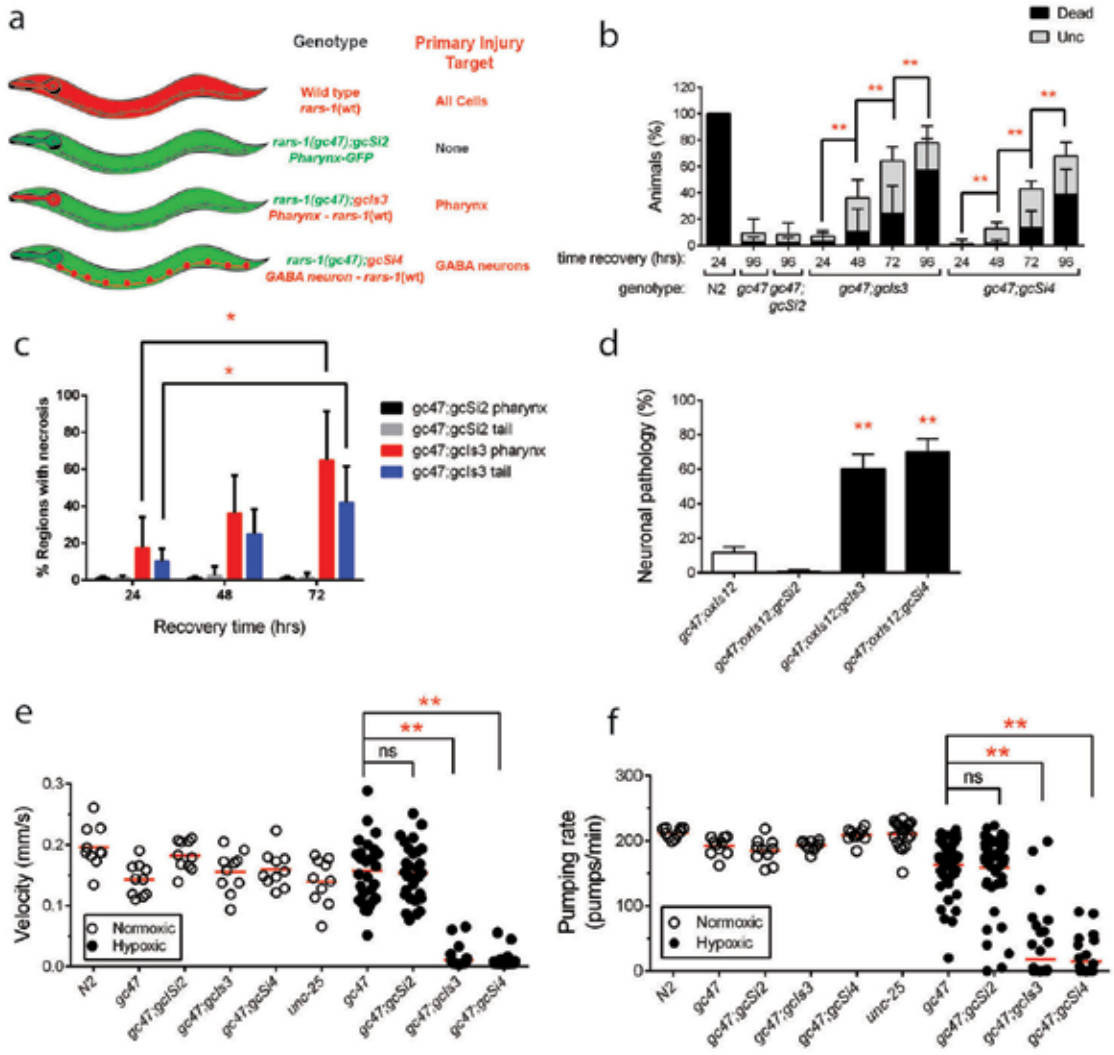
In stroke, neurons in the most severely hypoxic areas die rapidly while those in surrounding less hypoxic areas (termed the ischemic penumbra) may recover or have delayed cell death. The penumbral cells are the therapeutic target in stroke, but a genetically tractable model of the penumbra is lacking. Towards that end, we generated transgenic C. elegans strains where subsets of non-essential cells are made more sensitive to hypoxia than the remaining cells in the organism. The hypothesis is that this will produce animals where localized hypoxic injury will occur and then delayed injury of surrounding cells. We utilized a mutation (gc47) of the translation factor gene rars-1 that confers high level resistance to hypoxia in the nematode C. elegans (1), and into this mutant background, we integrated a transgene expressing wild type rars-1 only in pharyngeal myocytes or GABA neurons (Fig. 1a). After hypoxic incubations, both the pharyngeal myocyte-targeted and GABA neuron-targeted strains initially survive but then have progressive behavioral and cellular defects followed by significant animal death (Fig. 1a-d). Cells died by delayed necrosis (Fig. 1c). Injury and necrosis of non-targeted cells were prevalent as were off-target behavioral defects (Fig. 1c-f, eg. locomotion defects in pharyngeal-targeted or pumping defects in GABA neuron-targeted). We used the pharyngeal myocyte-targeted strain to answer two questions about a previously identified hypoxia resistance mutation (2): First, does the gene act to control non-targeted cell death when the mutation is not expressed in either the targeted or non-targeted cell type? Second, can manipulation of the gene activity only after hypoxic injury reduce delayed cell death? The data show that the answers to both questions are yes (data will be shown at meeting).

Summary: This unique model produces a delayed and secondary hypoxic cell death as is thought to occur in the ischemic penumbra and provides a powerful means to identify factors that ameliorate this type of injury.

Figure 1. Delayed and Secondary hypoxic cell injury/death in C. elegans. Bar graphs are means +/- SD of a minimum of 3 independent trials. ns-non significant,* - $p < 0.05$, ** $p<0.01$, 2-tailed test. a) Schematic of transgenic C. elegans strains generated for this study. b) Time course of onset of uncoordinated movement (Unc) and animal death after hypoxic incubation. c) Time course of appearance of severe necrosis (>5 cells) in either the pharynx or distant tail region. d) Neuronal pathology (axonal beading, breakage, distortion, or cell body loss) in GABA neurons 72 hours after hypoxia in alive animals. e) Velocity of locomotion of alive animals (normoxic or 72 hours after hypoxia), unc-25 is a mutant with no GABA. f) Pharyngeal pumping rate of alive animals (normoxic or 72 hours after hypoxia).

References:

1. Anderson LL, Mao X, Scott BA, Crowder CM. Science 323:630-3, 2009
2. Scott BA, Avidan MS, Crowder CM. Science 296:2388-91, 2002


a
Genotype
Primary Injury Target
Wild type
rars-1(wt)
All Cells
rars-1(gc47);gcSi2
Pharynx-GFP
None
rars-1(gc47);gcIs3
Pharynx - rars-1(wt)
Pharynx
rars-1(gc47);gcSi4
GABA neuron - rars-1(wt)
GABA neurons
b
Dead
Unc
Animals (%)
time recovery (hrs):
genotype:
N2
gc47;gcSi2
gc47;gcIs3
gc47;gcSi4
c
% Regions with necrosis
Recovery time (hrs)
gc47;gcSi2 pharynx
gc47;gcSi2 tail
gc47;gcIs3 pharynx
gc47;gcIs3 tail
d
Neuronal pathology (%)
gc47;oxIs12
gc47;oxIs12;gcSi2
gc47;oxIs12;gcIs3
gc47;oxIs12;gcSi4
e
Velocity (mm/s)
Normoxic
Hypoxic
ns
f
Pumping rate (pumps/min)
Normoxic
Hypoxic
ns

Oral Presentations

Zero Tolerance for Chronic Pain

Howard B. Gutstein, M.D.; Katherine Barker, Ph.D.; Shanping Shi, B.S.; Miguel Diaz, B.S.; Bing Mo, Ph.D.;
MD Anderson Cancer Center

For centuries, opioid drugs such as morphine have been the first-line treatment for chronic pain. However, over time tolerance to opioid analgesia develops, leaving few treatment options and leading to tremendous suffering for pain patients1. Here we show that platelet-derived growth factor receptor beta (PDGFR-)-mediated signaling is sufficient to cause morphine tolerance and necessary for its behavioral expression. We found that morphine activated PDGFR- in vitro and in vivo2. Behavioral studies showed that the clinically used PDGFR inhibitor imatinib completely eliminated and reversed morphine tolerance. If imatinib was subsequently discontinued, animals reverted to the tolerant state. Also, administration of the PDGFR-b agonist platelet-derived growth factor BB (PDGF-BB) rendered animals tolerant to subsequent morphine doses. Neither imatinib nor PDGF-BB affected tolerance development to the analgesic drug clonidine, an a-2 adrenoreceptor agonist, suggesting that tolerance modulation by PDGFR- was opioid-specific. Our results identify a specific cellular signal that selectively mediates morphine tolerance. Furthermore, imatinib is widely used to treat leukemia and gastrointestinal tumors, and clinically well-tolerated. This suggests that our findings could be rapidly translated into clinical practice, potentially reducing the tremendous suffering endured by patients in chronic pain.

Oral Presentations

Critical Role of Interleukin-11 in Isoflurane-Mediated Protection Against Ischemic Acute Kidney Injury

H.T. Lee, M.D., Ph.D.; Mihwa Kim, Pharm.D.; Ahrom Ham, Ph.D.; Joo Yun Kim, Ph.D.
Columbia University

Introduction: Acute kidney injury (AKI) is a major clinical problem without effective therapy (1). We demonstrated previously that isoflurane protects against renal ischemia-reperfusion (IR) injury by attenuating necrosis, apoptosis and inflammation (2). However, the isoflurane therapy for critically ill patients may be limited by its anesthetic and cardiovascular effects. One way to mitigate this is to utilize the distal signaling molecules synthesized with isoflurane treatment. Interleukin-11 (IL-11) is a clinically used hematopoietic cytokine that increases platelet count upon long term use (3). Recent studies suggest that IL-11 also attenuates necrosis, apoptosis and inflammation after intestinal, cardiac and renal IR injury (4). Here, we tested the hypothesis that isoflurane protects against ischemic AKI by direct induction of kidney IL-11 synthesis.

Methods: To test whether isoflurane induces renal proximal tubule IL-11 synthesis, human proximal tubule (HK-2) cells were treated with 1.25-2.5% isoflurane or carrier gas (room air+5% CO2) for 3-16 hr. We also anesthetized mice with 1% isoflurane or with equi-anesthetic dose of pentobarbital for 4 hr. To test the role of IL-11 in isoflurane-mediated renal protection, we subjected IL-11 receptor (IL-11R) wild type (WT) or deficient (KO) mice to 30 min renal ischemia followed by reperfusion under 4 hr of pentobarbital or isoflurane (1%) anesthesia. We also pretreated IL-11R WT mice with IL-11 neutralizing antibody or control isotype antibody (1 mg/kg i.p.) 30 min. before isoflurane anesthesia. Finally, we tested whether exogenous administration of recombinant human IL-11 (1 mg/kg s.c.) immediately before or 30 min after reperfusion mimics isoflurane-mediated protection against ischemic AKI.

Results: Isoflurane increased IL-11 mRNA (Fig. 1A) and protein in HK-2 cells (Fig. 1B). A specific inhibitor of ERK MAPK (PD98059) attenuated isoflurane-mediated induction of IL-11 in HK-2 cells (Fig. 1B). Mice anesthetized with isoflurane showed significantly increased kidney IL-11 mRNA (Fig. 1C) and protein expression (Fig. 1D) compared to pentobarbital anesthetized mice. Furthermore, IL-11R WT mice subjected to renal IR under pentobarbital anesthesia developed severe AKI with large increases in plasma Cr 24 hr after injury (Fig. 2). In contrast, IL-11R WT mice anesthetized with 1% isoflurane after renal ischemia had significantly reduced renal IR injury. Supporting a critical role of IL-11 in isoflurane-mediated renal protection, isoflurane failed to protect IL-11R KO mice against ischemic AKI. In addition, IL-11 neutralizing antibody abolished the renal protection provided by isoflurane in IL-11R WT mice. Finally, IL-11R WT mice treated with human recombinant IL-11 immediately before or 30 min after reperfusion were significantly protected against renal IR injury.

Conclusions: Taken together, our studies suggest that isoflurane induces renal tubular IL-11 to protect against ischemic AKI. Exogenous administration of IL-11 may have reduce the morbidity and mortality arising from AKI without the systemic effects of volatile anesthetics.

References

1. Contrib Nephrol 165: 1, 2010.
2. AJP Renal Physiol 293: F713, 2007.
3. Oncology (Williston Park) 14: 41, 2000.
4. AJP Renal Physiol 303: F1216, 2012.

Figure 1

Figure 1A

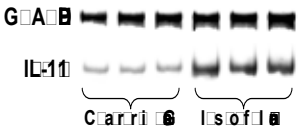


Figure 1C

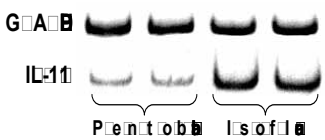


Figure 1B

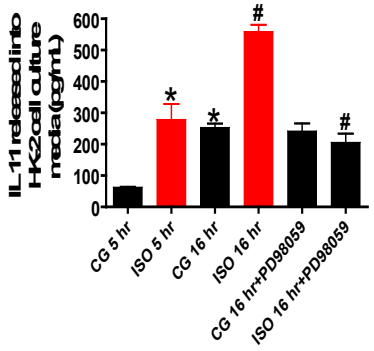


Figure 1D

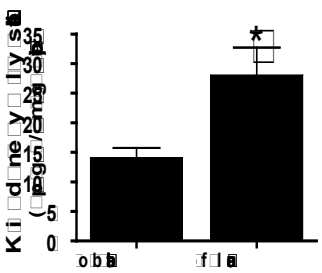


Figure 2

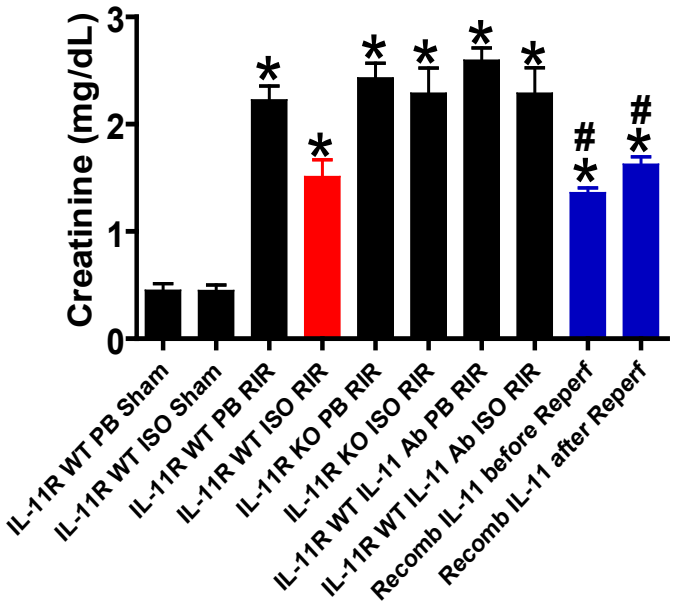


Figure 2. IL-11 is critical for isoflurane post-conditioning-mediated protection against ischemia AKI. Isoflurane post-conditioning failed to protect IL-11 receptor deficient mice or IL-11 receptor wild type mice treated with IL-11 neutralizing antibody against renal IR injury. Furthermore, recombinant human IL-11 given before or 30 min. after reperfusion protected against ischemic AKI. RIR – renal ischemia and reperfusion. IL-11R = Il-11 receptor, IL-11 ab = IL-11 neutralizing antibody, *P<0.05 vs. IL-11R WT PB Sham. #P<0.05 vs. IL-11R WT PR RIR. N=5-6 per group. Data represented as mean±SEM.

Oral Presentations

MicroRNAs and Anesthetic Cardioprotection in Diabetes

Zeljko J. Bosnjak, Ph.D.; Jessica Olson, M.S.; Alison Kriegel, Ph.D.; Xiaowen Bai, M.D., Ph.D.; Mingyu Liang, M.B., Ph.D.
Medical College of Wisconsin

Introduction: MicroRNAs are endogenous small RNA molecules that regulate a wide range of cellular functions primarily through reduction of target proteins. Several microRNAs have been shown to play important roles in cardiac injury,(1,2) and also contribute to the development of diabetic complications (3,4) and cardiac preconditioning.(5-7) We explored the contribution of microRNAs, since their role in anesthetic cardioprotection remains largely unknown. We utilized a model of the patient-specific induced pluripotent stem cells (iPSCs) differentiated into the cardiac lineage in order to delineate the environmental and cellular mechanisms responsible for overturning anesthetic cardioprotection in diabetes. We hypothesized that miR-21 contributes to cardioprotection conferred by anesthetics in human cardiomyocytes and that diabetic conditions compromise this protection in part via suppression of miR-21.

Methods: We have developed and validated a clinically relevant model of cardioprotection using human cardiomyocytes differentiated from the iPSCs derived from non-diabetic individuals (N-CM) and patients with type 2 diabetes mellitus (T2-CM).(8,9) The advantage of this approach is that the effect of anesthetics can be evaluated in human cardiomyocytes, thereby, capturing the complex physiologic interactions at the patient-specific myocyte level.

Results: Our results indicate that cardiomyocytes derived from type 2 diabetes-specific stem cells recapitulate the phenotypic findings from type 2 diabetic patients. For instance, T2-CM exhibited a suppression of protein kinase B (Akt) and activation of glycogen synthase kinase-3 (GSK-3), compared to N-CM; indicating that this pathway is compromised in cardiomyocytes derived from diabetic individuals (Fig.1). Similar findings were reported in the diabetic individuals.(10) In addition, we examined whether isoflurane could delay oxidative stress-induced mitochondrial permeability transition pore (mPTP) opening in T2-CM and found that the effects of isoflurane were significantly attenuated as compared to N-CM (Fig.2). Finally, isoflurane increased miR-21 abundance in N-CM, but not in T2-CM (Fig.3). The increase of miR-21 abundance was completely lost even in N-CM pre-treated with high ambient glucose.

Summary: Diabetes and hyperglycemia substantially increase perioperative cardiovascular risk, with few mitigating strategies. Our data indicate an important role of miR-21 in isoflurane-induced cardioprotection and its impairment by diabetic conditions that may suggest new therapeutic targets for reducing perioperative cardiovascular morbidity and mortality in high-risk patients.

References: 1)Nature.2011;469(7330):336-42; 2)Circ Res.2009;104(6):724-32; 3)Diabetes.2011;60(7):1825-31; 4) Diabetes.2011;60(7):1832-7; 5) J Biol Chem.2009;284:29514-25; 6) Cardiovasc Res.2010;87(3):431-9; 7)Circ Res.2009;104(5):572-5; 8) Anesthesiology.2010;113:906-16; 9)Anesthesiology.2012;117:735-44; 10)J Cell Moll Med.2010;14:1740-6.

Oral Presentations

Percutaneous Fiber Optic Monitoring for Spinal Cord Ischemia

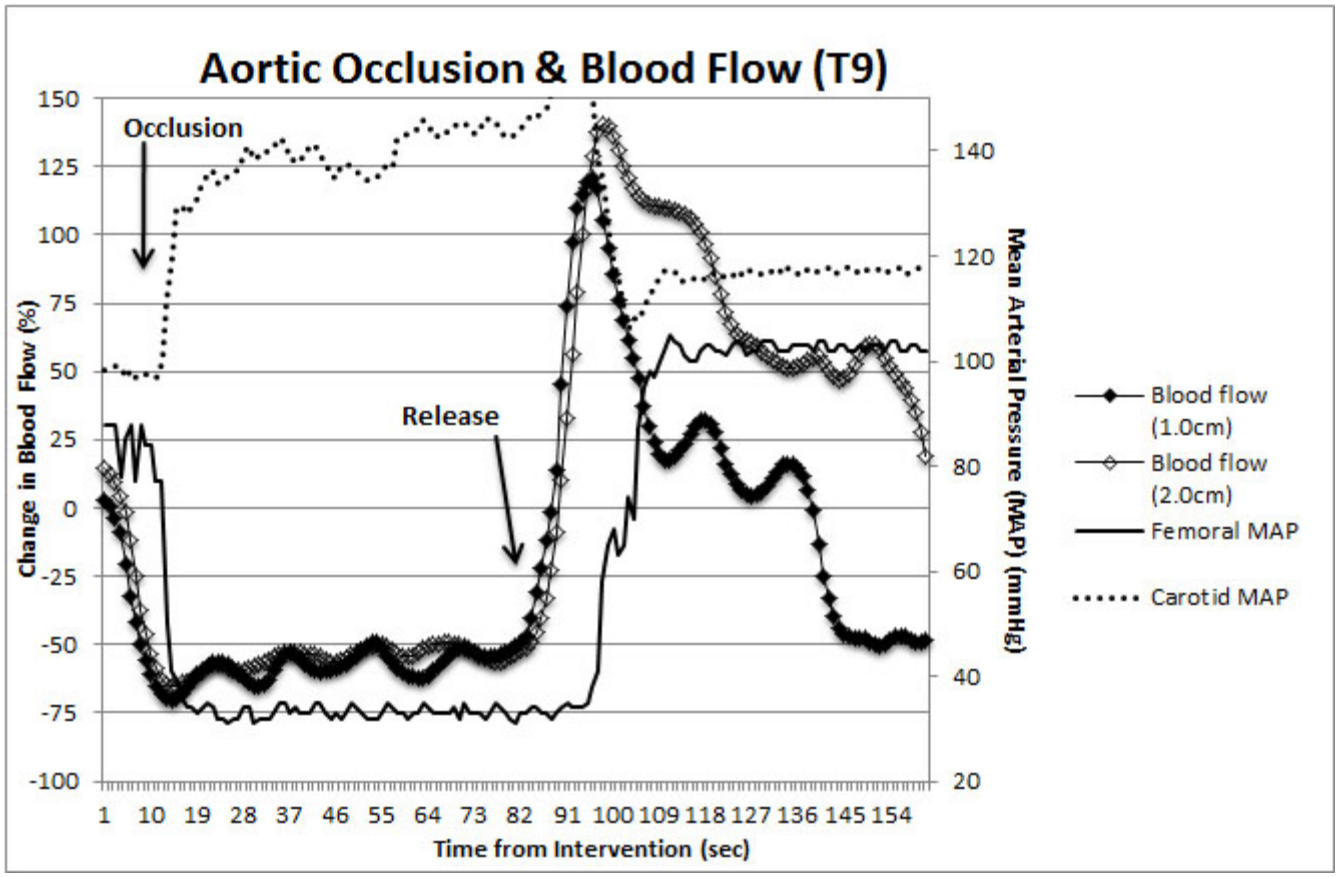
Angela D'Souza, M.S., BME[1]; Rickson Mesquita, Ph.D.[2]; Thomas V. Bilfinger, M.D.[1]; Robert M. Galler, D.O.[1]; Arjun Yodh, Ph.D.[2]; Thomas F. Floyd, M.D.[1]
Stony Brook University[1]; University of Pennsylvania[2]

Introduction: Spinal cord ischemia may result in paralysis and paraparesis after trauma, major vascular, spine and spinal cord surgery. Current methods employed to detect spinal cord ischemia, based upon electrophysiology, are indirect, temporally insensitive, nonspecific, and cumbersome.

Methods: We have developed a prototypical fiber optic device based on Diffuse Correlation Spectroscopy (DCS) and Diffuse Optical Spectroscopy (DOS) principles that allow for the detection of changes in spinal cord blood flow and oxygenation. The device has been tested in Dorsett sheep. We employed a linearly arrayed clinical prototype, with a single source and two detectors. Under general anesthesia, femoral and carotid arterial lines were placed. An intra-aortic balloon was advanced to the common cephalic root. A left atrial catheter was placed for the injection of microspheres for quantification of spinal cord blood flow by a proven standard. The fiber optic probe was introduced into the epidural space via Touhy needle and advanced cephalad under fluoroscopic guidance. Spinal cord blood flow and oxygenation responses to pharmacologic interventions (phenylephrine-400ug boluses and nitroprusside-400ug boluses) and aortic occlusion were measured at multiple levels. Spinal cord blood flow and oxygenation were recorded continuously via the fiber optic probe.

Results: The fiber optic probe immediately detected increased blood flow and oxygenation in response to hypertension, and decreased flow and oxygenation in response to hypotension. Aortic occlusion resulted in an immediate fall in spinal cord blood flow and oxygenation. Previous work in our lab has demonstrated blood flow responses from subdural, epidural, or percutaneously placed probes to be indistinguishable. Blood flow measurements from the DCS probe were directionally in agreement yet more robust than measurements obtained from microsphere measurements. Data from this and previous experiments demonstrates that the fiber optic probe is sensitive, successfully detecting changes in spinal cord blood flow associated with acute hypertension in 12/12 trials (100%), acute hypotension in 9/9 trials (100%), aortic clamping in 14/14 trials (100%), and selective ligation of vertebral arteries in 1/1 trial. In a series of experiments, the mean change in flow associated with the hypertensive and hypotensive challenges was (+) 51 ± 11% and (-) 39 ± 11% respectively. The instantaneous flow:pressure response correlation was $R2 = 0.92$, $p < .001$. Rapid pressure autoregulation was seen with pressure changes >≈ 50 torr.

Conclusions: Percutaneous fiber optic monitoring of spinal cord blood flow and oxygenation is feasible and the results of initial testing are promising. This monitoring tool potentially represents an important step forward, offering a new level of accuracy and immediacy in detecting spinal cord ischemia intraoperatively, and in the neurocritical care setting.



Poster Presentations

Clinical/Basic Neuroscience

CBN 1(18)

Influence of Equivalent Dose of Propofol & Sevoflurane on rCBF - fMRI, ASL Study in Volunteers
Ramachandran Ramani, M.B.B.S., M.D.; Maolin Qiu, Ph.D.; Robert Todd Constable, Ph.D.
Yale University School of Medicine

CBN 2 (29)

Improvement in Endothelial Function is Associated with Reduced Brain Dysfunction in Critically Ill Patients
Christopher G. Hughes, M.D.; Nathan E. Brummel, M.D.; Timothy D. Girard, M.D.; Amy J. Graves, MPH; E. Wesley Ely, M.D.; Pratik P. Pandharipande, M.D.
Vanderbilt University School of Medicine

CBN 3 (30)

The Long Term Effects on Cognition and Development of Post-traumatic Stress Disorders in Critically Ill Children: A Pilot Study
Heidi A.B. Smith, M.D., MSCI[1]; Jenna M. Sopfe, M.D.[2]; Stacey L. Doran, MSIV[1]; Daniel O. Fishman, MSIV[1]; James M. Kynes, M.D.[1]; Pratik P. Pandharipande, M.D., MSCI[1]
Vanderbilt University[1]; University of Colorade School of Medicine[2]

CBN 4 (31)

Cognitive Dysfunction and Early Mortality Following Carotid Endarterectomy
Eric J. Heyer, M.D., Ph.D.; Joanna L. Mergeche, B.A.; Joanne Brady, M.S.; Charles J. DiMaggio, Ph.D.; Samuel S. Bruce, M.S.; E. Sander Connolly, M.D.
Columbia University

CBN 5 (59)

Functional Neuroimaging of Sevoflurane-induced Unresponsiveness Reveals Reorganized Resting-State Networks and Reduced Global Connectivity
Ben Julian A. Palanca, M.D., Ph.D.; Benjamin J. Shannon, Ph.D.; Abraham Z. Snyder, M.D., Ph.D.; Alex S. Evers, M.D.; Michael S. Avidan, M.B.B.S.; Marcus E. Raichle, M.D.
Washington University School of Medicine

CBN 6 (74)

Resident Travel Award
Stimulation of Stimulation of Î±2-Adrenergic Receptors Antagonizes Isoflurane-induced Activation of Sleep-promoting VLPO Neurons and Partially Attenuates Anesthetic Hypnosis
Michael R. Chalifoux, M.D.; Hilary McCarren, B.S.; Bo Han, M.D., Ph.D.; Matthew Fleisher; Sheryl Beck, Ph.D.; Max Kelz, M.D., Ph.D.
University of Pennsylvania

CBN 7 (80)

A Neurophysiological Approach to Electroencephalogram Monitoring During General Anesthesia and Sedation
Patrick L. Purdon, Ph.D.[1,2]; Aaron L. Sampson, B.S.[1]; Emery N. Brown, M.D., Ph.D. [1,2,3]
Massachusetts General Hospital[1]; Harvard Medical School[2]; Massachusetts Institute of Technology[3]

CBN 8 (81)

CSF Markers of Alzheimers Disease After Propofol or Isoflurane Anesthesia (MAD-PIA): Preliminary Results From a Human Randomized Controlled Trial.
Miles Berger, M.D., Ph.D.; David McDonagh, M.D.; Mark Newman, M.D.; Joseph Mathew, M.D.; Michael James, M.D.
Duke University Medical Center

CBN 9 (25)

Barking Up the Wrong Tree - Why Anesthetic Mechanism Research Has Failed, and How to Fix It
Stuart Hameroff, M.D.
Department of Anesthesiology, University of Arizona Medical Center

CBN 10 (27)

Modeling the Ischemic Penumbra in C. Elegans
C. Michael Crowder, M.D., Ph.D.; Chun-Ling Sun, Ph.D.; Euysoo Kim, Ph.D.
Washington University School of Medicine

CBN 11 (34)

The Role of Mast Cells in the Pathophysiology of Intracranial Aneurysm
Tomoki Hashimoto, M.D.
University of California, San Francisco

CBN 12 (48)

Junior Faculty Award
Optogenetic Stimulation of Dopamine Neurons in the Ventral Tegmental Area
Norman E. Taylor, M.D., Ph.D.[1]; Christa J. Van Dort, Ph.D.[1]; Jonathan Kenny, B.S.[1]; Emery N. Brown, M.D., Ph.D.[1,2]; Ken Solt, M.D.[1]
Massachusetts General Hospital[1]; Massachusetts Institute of Technology[2]

Poster Presentations

Clinical/Basic Neuroscience *(cont.)*

CBN 13 (53)

Lidocaine Block of Mutant Rat Skeletal Muscle Na+ Channels Lacking Fast Inactivation: Open Channel Block as a Priming Mechanism for Long-Lived Inactivated Block

Kevin J. Gingrich, M.D.[1]; Larry Wagner, M.S.[2]
UT Southwestern Medical Center[1]; University of Rochester Medical Center[2]

CBN 14 (57)

General Anesthetic Interactions with Beta Tubulin Contributes to the Immobility Endpoint

Roderic G. Eckenhoff, M.D.; Daniel J. Emerson, B.S.; Brian P. Weiser, B.S.; Amos B. Smith, Ph.D.; Ivan J. Dmochowski, Ph.D.
University of Pennsylvania Perelman School of Medicine

CBN 15 (72)

Role of Soluble Epoxide Hydrolase in Exacerbation of Stroke by Type 2 Diabetes Hyperglycemia in Mice

Robert E. Shangraw, M.D., Ph.D.; Kristen Zuloaga, Ph.D.; Stephanie M. Krasnow, Ph.D.; Wenri Zhang, M.D.; Daniel L. Marks, M.D., Ph.D.; Nabil J. Alkayed, M.D., Ph.D.
Oregon Health & Science University

Influence of Equivalent Dose of Propofol & Sevoflurane on rCBF - fMRI, ASL Study in Volunteers

Ramachandran Ramani, M.B.B.S., M.D.; Maolin Qiu, Ph.D.; Robert Todd Constable, Ph.D.
Yale University School of Medicine

Introduction: BOLD (Blood Oxygen Level dependent contrast) is a measure of neuronal activity in the brain in fMRI. Regional CBF (rCBF) also reflects neuronal activity because of the flow metabolism coupling in the brain. The caveat is while this is true for intravenous anesthetics volatile anesthetics have a direct vasodilatory effect on the cerebral vasculature which can decrease the metabolism induced decrease in rCBF. This net effect on rCBF influences both cerebral blood volume as well as the ICP. There are studies which suggest that at doses < 0.5 MAC sevoflurane the indirect effect on rCBF related to flow metabolism coupling is more dominant. This is important because of its clinical significance (effect on ICP) and in the interpretation of rCBF studies on CNS effects of anesthesia. With this background in the present study we compared the rCBF effects of plasma level of 2µg/mL of propofol with equivalent dose of sevoflurane in healthy volunteers.

Methods: The study protocols were approved by the Yale University HIC. The propofol study subjects were 19 healthy ASA 1 volunteers (19-35 years old). Subjects were monitored as per ASA monitoring standard and propofol anesthesia was administered through a TCI device (Stanpump pump). TCI propofol level was 2 µg / mL. Blood propofol level was measured at the beginning and end of the infusion period. Regional CBF was measured in a 3 Tesla Siemens Trio by the PASL technique. CBF was measured in the awake state as well as anesthesia. Similar protocol was followed in the sevoflurane study (13 subjects). Anesthesia was administered through a face mask. A mixture of oxygen and sevoflurane (1% = 0.5 MAC) was administered through a circle absorber circuit (spontaneous ventilation). The difference in rCBF (ΔCBF) between awake and anesthesia state was calculated in both the studies. Regions of interest (ROI's) were identified using the Talairache co-ordinates.

Results: Clinically with 0.5 MAC equivalent dose both propofol as well as sevoflurane induced a state of sleep where the OAAS score was ≤ 2 (no response to call) in all subjects and none had any memory of the events. Vital signs were within physiological limits in both the studies. Propofol induced a significant drop in rCBF in the major cortical regions (frontal, parietal, temporal & occipital lobe as well as the thalamus). There was a rise in rCBF in the anterior cingulate, insula & para hippocampal gyrus. With sevoflurane there was a decrease in rCBF in the frontal, occipital, cingulate and thalamic cortical regions. In the hippocampus there was a rise in rCBF while temporal cortex had regions with increase as well as decrease in CBF.

Discussion: While both propofol and sevoflurane decreased rCBF in most cortical regions propofol effect was predominantly in the neocortex. Frontal, occipital and thalamic regions are affected by both anesthetics. In addition propofol also affects the parietal & temporal cortex. A PET scan CMRg study reported similar effect with 1MAC propofol as well as sevoflurane[1]. There were no regions with rise in CMRg with both. Jeong et al compared 0.5 MAC propofol with sevolfurane (CMRg) and reported predominantly cortical effect with propofol[2]. And there was rise in rCBF in the cing

Improvement in Endothelial Function is Associated with Reduced Brain Dysfunction in Critically Ill Patients

Christopher G. Hughes, M.D.; Nathan E. Brummel, M.D.; Timothy D. Girard, M.D.; Amy J. Graves, MPH; E. Wesley Ely, M.D.; Pratik P. Pandharipande, M.D.
Vanderbilt University School of Medicine

Introduction: Endothelial dysfunction has been independently associated with prolonged brain dysfunction (delirium and coma) during critical illness, a syndrome that leads to increased length of stay, mortality, and long-term cognitive dysfunction.(1-5) It is unknown if improvement in endothelial function over time is associated with reduced brain dysfunction in these patients. Physical therapy (PT) reduces delirium in the ICU and improves endothelial function in outpatients.(6;7) We hypothesized that improvement in endothelial function in ICU patients is associated with less brain dysfunction [more delirium/coma-free days (DCFDs)] and that early PT in the ICU is associated with improvement in endothelial function.

Methods: This prospective cohort study was nested within a randomized trial of early PT versus usual care in adult medical/surgical ICU patients with shock or respiratory failure. Endothelial function was assessed at enrollment and at 7 days or hospital discharge via peripheral artery tonometry reactive hyperemia index (RHI), with lower RHI indicative of worse endothelial function.(8) Coma and delirium were assessed daily using the Richmond Agitation-Sedation Scale and Confusion Assessment Method for the Intensive Care Unit.(9;10) Multivariable linear regression was used to study the associations of enrollment RHI and changes in RHI with DCFDs over a 14-day period, adjusting for PT and sepsis. We further examined whether PT was associated with increases in RHI and whether PT modified the association between enrollment RHI and DCFDs.

Results: RHI was measured at enrollment in 72 of the 87 patients in the parent study; 42 had RHI measured at both time points. The mean age was 59 years, mean APACHE II was 25, 44% were admitted with severe sepsis, and mean DCFDs were 9 days. Worse enrollment RHI was independently associated with fewer DCFDs ($p<0.001$), and improvement in RHI over time was associated with increased DCFDs, such that a patient with 0.7 improvement in RHI would have, on average, 1.9 greater DCFDs over the 14-day study period ($p=0.02$, Figure 1). PT was marginally associated with improvement in endothelial function ($p=0.09$), but PT did not modify the association between enrollment RHI and DCFDs (p for interaction=0.8).

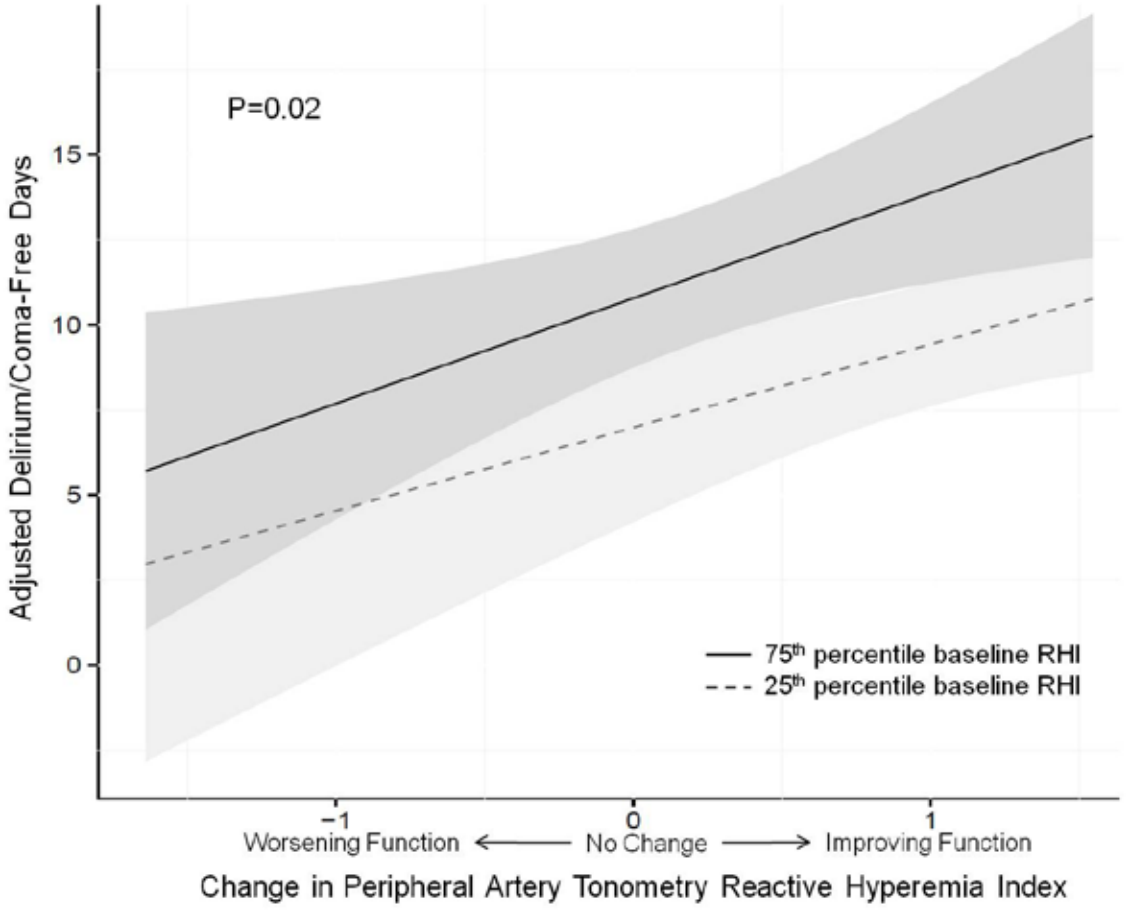
Conclusion: These data support that endothelial dysfunction is an important prognostic marker of acute brain dysfunction in ICU patients and that improving endothelial function (whether spontaneous or through a future intervention) may reduce the duration of acute brain dysfunction.

References

1. Hughes CG et al. Anesthesiology 2012 Dec 19; epub
2. Ely EW et al. Intensive Care Med. 2001 Dec;27(12):1892-900
3. Ely EW et al. JAMA 2004 Apr 14;291(14):1753-62
4. Girard TD et al. Crit Care Med. 2010 Jul;38(7):1513-20
5. Shehabi Y et al. Crit Care Med 2010 Dec;38(12):2311-8
6. Schweickert WD et al. Lancet 2009 May 30;373(9678):1874-82
7. Haram PM et al. Front Biosci 2008;13:336-46
8. Kuvin JT et al. Am Heart J 2003 Jul;146(1):168-74
9. Sessler CN et al. Am J Respir Crit Care Med 2002 Nov 15;166(10):1338-44
10. Ely EW et al. JAMA 2001 Dec 5;286(21):2703-10

Extra Files:

Figure 1. Change in Endothelial Function vs. Delirium/Coma-Free Days



The Long Term Effects on Cognition and Development of Post-traumatic Stress Disorders in Critically Ill Children: A Pilot Study

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Background: Critically ill children suffer from post-traumatic stress disorder and deficits in attention, and spatial and verbal memory, following discharge. The impact of critical illness on executive function, which is necessary for purposeful, goal-directed, and problem-solving behavior in addition to higher learning, has not been studied in children. Objective: To determine the prevalence of executive dysfunction and PTSD in children following critical illness, and identify specific risk factors for the development of executive dysfunction.

Methods: In this prospective cohort study, we enrolled patients aged 5-17 years admitted to the pediatric intensive care unit (PICU) with 1 of the following: mechanical ventilation (MV), vasopressor therapy, a Pediatric Risk of Mortality (PRISM III) score over 15, or a neurologic admission diagnosis. We collected demographic data at enrollment and in-hospital data until PICU discharge. Our primary outcome was executive function, which is measured by the Behavior Rating Inventory of Executive Function (BRIEF). The BRIEF was completed upon enrollment and then at 3 and 6 months following discharge. The BRIEF assesses 8 domains of executive function and is reported as a Global Executive Composite (GEC) T-score. For the GEC, a T-score of 50 reflects the age/gender adjusted norm for that population, and a 10 point increase indicates a 1-standard deviation (SD) worsening in outcome. The Child PTSD Symptom Scale was completed in children at least 8 years of age. Linear regression assessed the relationship between duration of mechanical ventilation with GEC outcomes at 3 months and 6 months separately, adjusting for a priori determined covariates (PRISM and baseline GEC scores).

Results: The median PRISM score for the 99 patients enrolled was 6 (2.5, 11) reflecting moderate illness, with 67.7% of patients requiring MV. Median executive function scores (GEC) were 0.5 SD worse than population norms at 3 months [54.6 (p=0.1)] and 6 months [57.1 (p=0.08)] following discharge, though were not significantly different from baseline. In MV patients, however, the GEC was significantly worse at 3 months compared to baseline (p=0.03). For descriptive purposes the 8 subdomains of executive function were analyzed. In our cohort, working memory was significantly worse at 3 months [T-score 55.8 (p=0.02)], and the ability to initiate thought was significantly worse only at 6 months [T score 55.9 (p=0.03)] when compared to baseline. Among patients requiring MV, working memory was significantly worse at 3 months [T-score 55.8 (p=0.01)], and the ability to initiate thought was significantly worse at 3 months [T-score of 52.5 (p=0.03)] and 6 months [53.9 (p=0.05)] following discharge. In patients > 8 years, PTSD occurred in 7% of patients at 3 months, with only 5% having ongoing symptoms at 6 months. In our multivariable regressions, baseline executive function was the strongest predictor of worse GEC scores at 3 and 6 months.

Conclusions: Children suffer from cognitive dysfunction and PTSD following critical illness. Larger studies are needed to determine the prevalence of these serious morbidities and to identify potentially modifiable risk factors to target interventional therapies.

Cognitive Dysfunction and Early Mortality Following Carotid Endarterectomy

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Background: Cognitive dysfunction is a subtler form of perioperative neurologic injury than stroke. It is observed in approximately 25% of patients undergoing carotid endarterectomy (CEA)1,2. This study aims to determine whether early cognitive dysfunction within 1 day of CEA is associated with increased risk of early mortality compared to patients without cognitive dysfunction.

Methods: Five hundred fifty-one (551) consecutive patients with carotid artery stenosis undergoing elective CEA between 1995 and 2012 were enrolled with written informed consent in this IRB-approved observational study. All patients were evaluated with a battery of neuropsychometric tests for cognitive dysfunction pre-operatively and 1 day post-operatively. Patients with cognitive dysfunction at this time were considered to have early cognitive dysfunction. All patients were followed until 2012. The risk of mortality was assessed using Kaplan-Meier methods and multivariable Cox proportional hazards models.

Results: One hundred seventy-eight (178, 32.3%) people died during the study period. The median survival for patients that exhibited cognitive dysfunction within 1 post-operative day was 12.5 years vs. 15.9 years for patients without early cognitive dysfunction (χ^2=2.6, P=0.11). After adjusting for age, diabetes mellitus, and statin use, patients with early cognitive dysfunction had a risk of mortality (adjusted hazard ratio (aHR) 1.23, 95% confidence interval (CI) 0.09–1.69). In stratified multivariable models, patients with early cognitive dysfunction taking statins had an adjusted hazard ratio of 0.88 (95% CI 0.52–1.48). By comparison, patients with early cognitive dysfunction not taking statins had an adjusted hazard ratio of 1.61 (95% CI 1.07–2.42).

Conclusions: This study is the first to demonstrate that early cognitive dysfunction is associated with increased risk of earlier mortality than patients without cognitive dysfunction, particularly in patients not taking statins (Figure 1). This finding validates cognitive dysfunction as an important neurologic outcome, and suggests that preoperative medical management with statins may improve long-term survival.

References:

1. Heyer E, Adams D, Todd G, et al. Neuropsychometric changes in patients after carotid endarterectomy. Stroke; a journal of cerebral circulation. 1998;29(6):1110-1115.
2. Heyer EJ, Sharma R, Rampersad A, et al. A controlled prospective study of neuropsychological dysfunction following carotid endarterectomy. Archives of neurology. Feb 2002;59(2):217-222.

Figure 1. Bivariable Kaplan-Meier Plot – Patients Not Taking Statins.

Functional Neuroimaging of Sevoflurane-induced Unresponsiveness Reveals Reorganized Resting-state Networks and Reduced Global Connectivity

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Background: The weakening of synchronized neural activity distributed across the brain is a putative mechanism for the disruption of cognitive functions by anesthetic agents. Propofol sedation disrupts intrinsic attention networks linking neurons of frontal, parietal, and temporal regions [1]. Sevoflurane sedation weakens inter-hemispheric connectivity among motor regions [2] but its effects on attention networks remain equivocal [3]. The purpose of our study was to determine how sevoflurane disrupts cortical and subcortical network connectivity given its distinct molecular pharmacology relative to propofol.

Methods: Simultaneous electroencephalography and functional magnetic resonance imaging (fMRI) data were acquired from fifteen healthy human participants. The spontaneously breathing volunteers were imaged at baseline and during administration of 0.6% for sedation and 1.2% for rendering unresponsiveness. The correlation strengths among brain regions (functional connectivity) were calculated from volumes sampling the thalamus, caudate, putamen, and cerebellum; and across the default mode, dorsal attention, salience, and frontoparietal control networks. Significance of functional connectivity changes were assessed by permutation tests at a region level and paired t-tests at a network level.

Results: Sedation at 0.6% sevoflurane strengthened the connectivity among attention networks without significant effects within individual networks. The unresponsiveness of 1.2% sevoflurane was associated with widespread weakening of connectivity within and among cortical attention networks and among subcortical structures. Residual functional connectivity remained but did not respect the topology of intrinsic attention networks.

Conclusion: The transition from wakefulness to unresponsiveness of sevoflurane sedation is associated with a biphasic perturbation in cortical and subcortical functional connectivity and a reorganization of network dynamics in a manner more complex than a global weakening of correlated brain activity with increasing sevoflurane dose and are distinct from the effects of propofol.

References:

1. Boveroux, P., et al., Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology, 2010. 113(5): p. 1038-53.
2. Peltier, S.J., et al., Functional connectivity changes with concentration of sevoflurane anesthesia. Neuroreport, 2005. 16(3): p. 285-8.
3. Martuzzi, R., et al., A whole-brain voxel based measure of intrinsic connectivity contrast reveals local changes in tissue connectivity with anesthetic without a priori assumptions on thresholds or regions of interest. Neuroimage, 2011. 58(4): p. 1044-50.

Resident Travel Award

Stimulation of Stimulation of Î±2-Adrenergic Receptors Antagonizes Isoflurane-Induced Activation of Sleep-promoting VLPO Neurons and Partially Attenuates Anesthetic Hypnosis

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The ventrolateral preoptic (VLPO) nucleus of the hypothalamus plays a significant role in both sleep and anesthetic-induced hypnosis.[1] We have previously shown that the volatile agent, isoflurane (ISO), directly depolarizes sleep-promoting VLPO neurons while not affecting neighboring non-sleep-promoting VLPO neurons.[2] However, in the acute setting, the behavioral significance of sleep-promoting VLPO activation remains unknown.[2,3] If anesthetic-induced depolarization of sleep-promoting neurons were essential to hypnosis, then hyperpolarizing these neurons should attenuate the hypnotic state. We hypothesize that local pharmacologic treatment of sleep-promoting VLPO with dexmedetomidine (DEX) will antagonize both isoflurane-induced depolarization as well as its behavioral hypnosis in intact animals.

Using hypothalamic slices prepared from wild type C57BL6J mice, whole-cell current clamp recordings were conducted. VLPO neurons were classified as putative sleep-promoting based upon a hyperpolarizing response to a bath application of 100µM norepinephrine (NE).[2,4,5] To determine the mechanism of adrenergic-induced hyperpolarization, the highly potent and specific 2A adrenergic agonist, DEX, was bath-applied. In 7/7 putative sleep-promoting VLPO neurons, 100nM DEX also caused a hyperpolarization (-43 ± 2.7mV resting membrane potential (RMP) to -50 ± 2.3mV DEX, p=0.0014). Sleep-promoting VLPO neurons exposed to 330µM ISO alone depolarized (-48.6 ± 2.1mV RMP to -39.9 ± 4.1mV ISO, p=0.0004) and increased firing rates (0.06 ± 0.09Hz baseline to 0.5 ± 0.44Hz ISO, p=0.0112) in 6/6 cells. Concomitant administration of 100nM DEX plus 330µM ISO hyperpolarized the membrane (-39.9 ± 4.1 mV RMP to -45.98 ± 4.32mV DEX+ISO, p=0.0004) and decreased the firing rates (0.5 ± 0.44Hz ISO to 0.04 ± 0.09Hz DEX+ISO, p=0.0112) of all 6 neurons; thus reversing ISO's effects.

In 3/3 non-sleep-promoting, NE depolarized VLPO neurons, DEX did not significantly alter membrane potential or firing. Multiplex RT-PCR performed on single-cell cytoplasmic aspirates harvested from sleep-promoting VLPO neurons upon completion of electrophysiologic recordings,[6] confirmed the presence of 2A, 2B, and 2C adrenoceptors in DEX-hyperpolarized neurons.

To determine the functional significance of DEX's actions in VLPO, indwelling bilateral cannulae were used to deliver 25nl of adrenergic ligands into VLPO of mice stably anesthetized at 0.8% ISO or 500µm more caudally. During the 10 minutes prior to and 5 minutes following drug infusion, arousal state behavioral scores ranging from 0 (no movement) to 4 (full return of righting reflex) were assigned.[7] DEX delivered to VLPO caused a significant increase in arousal, while no change was observed with saline or the 1 agonist phenylephrine infusion in the same animals ($p<0.05$). Mice with more caudally placed cannulae exhibited no change in arousal with any drug. Though DEX nanoinjections in VLPO were able to arouse lightly anesthetized animals, no effects were seen in animals exposed to 1% ISO. These results suggest a significant contribution of adrenergic receptor signaling in VLPO in modulating hypnosis and builds upon the shared neuronal framework for sleep neurobiology and anesthetic mechanisms.

A Neurophysiological Approach to Electroencephalogram Monitoring During General Anesthesia and Sedation

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General anesthetic and sedative drugs induce stereotyped changes in the electroencephalogram (EEG) that were first observed in the 1930's, providing the basis for present day anesthetic brain monitors. The most popular approach to EEG-based anesthesia monitoring has been to use empirically-derived indices that reduce the EEG to a single number between 0 an 100. Although these indices are constructed from the EEG, they do not relate directly to the neurophysiology underlying each anesthetic drug's effects on the brain and the EEG, and thus cannot provide a completely accurate picture of a patient's brain state or level of consciousness. Moreover, anesthetic and sedative drugs are known to act through different mechanisms, producing different states of altered arousal, and different EEG patterns or signatures, which are poorly characterized by a single number. These fundamental mechanistic differences are evident when these indices are used with ketamine or nitrous oxide, which can elevate index values, or with dexmedetomidine, which can produce index values mimicking general anesthesia in patients who are merely sedated and can be easily aroused.

These mechanistic differences suggest an alternative approach: anesthesiologists could be trained to recognize the EEG signatures for different anesthetic drugs, allowing them to monitor the specific dose-dependent effects associated with each drug. In this abstract, we present this idea in two parts. The first part provides a means to easily recognize the EEG signatures for different anesthetic and sedative drugs based on the spectrogram, which characterizes the frequency content of signals over time. We recorded EEG during routine anesthetic brain monitoring in over 200 patients receiving different anesthetics, and performed spectral analysis to construct signatures for each anesthetic drug (Figure 1A). It is difficult to assess from unprocessed EEG waveforms the subtle changes that distinguish different anesthetics and dose levels. However, using spectrograms (Figure 1A; time on the x-axis, frequency on the y-axis, and energy in color), different drug- and dose-dependent effects are easily visualized. These spectral signatures can be visualized on many existing EEG devices, and their structure can be understood in terms of each drug's underlying mechanisms. The second part provides a means to assess level of unconsciousness based on patterns of modulation between slow oscillations and higher-frequency activity. One pattern, "peak-max," where high-frequency activity is greatest at the peaks of slow oscillations, represents a profound state of unconsciousness where cortico-cortico communications are fragmented, making awareness highly unlikely (Figure 1C,E) [1,2]. Another pattern, "trough-max," where high-frequency activity is greatest at the troughs of slow oscillations, appears prior to the return of consciousness, and reflects activity in circuits mediating arousal and executive function (Figure 1B,D) [1]. This trough-max pattern could be used to predict when patients can recover consciousness. Together, these EEG signatures suggest a precise, physiologically-principled alternative to index-based monitoring.

1. Purdon, et al., PNAS, in press; 2. Lewis, et al., PNAS 2012 109(49):E3377-86

CSF Markers of Alzheimers Disease After Propofol or Isoflurane Anesthesia (MAD-PIA): Preliminary Results From a Human Randomized Controlled Trial

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Introduction: Millions of Americans develop post-operative cognitive decline (POCD) or delirium after surgery/anesthesia each year. The cause of POCD and/or delirium is unknown, but there are similarities between Alzheimer's disease (AD), POCD and delirium. Inhaled anesthetics increase the phosphorylation of the microtubule-associated protein tau in animal models and cell culture (1), similar to the increase in tau phosphorylation seen in AD. Similar changes have been found in patients after anesthesia/surgery (2). To examine whether tau phosphorylation increases specifically after isoflurane versus propofol anesthesia in patients we have initiated the Duke IRB approved MAD-PIA trial- Markers of Alzheimer's Disease after Propofol or Isoflurane Anesthesia. Here we present the initial results from this trial on tau phosphorylation and total tau levels.

Methods: Patients undergoing neurosurgical procedures requiring lumbar CSF drain placement were prospectively consented, enrolled and randomized to isoflurane versus propofol anesthesia. CSF samples were obtained at induction of anesthesia, and again three hours later. CSF samples were assayed for tau phosphorylation (and total tau levels) by xMAP multiplex immunoassays.

Results: CSF tau increased from 42.1 +/- 9.9 pg/ml at induction to 45.6 +/- 7.4 pg/ml three hours later in isoflurane treated patients (N=13), and from 56.5 +/-21.9 pg/ml at induction to 76.5 +/- 36.5 pg/ml three hours later in propofol treated patients (N=6). CSF phospho-tau increased from 30.2 +/- 4.2 pg/ml at induction to 34.4 +/- 5.2 pg/ml three hours later in isoflurane treated patients, and from 22.6 +/- 2.4 pg/ml at induction to 23.5 +/- 5.0 pg/ml three hours later in propofol treated patients. There was no difference between CSF tau or phospho-tau levels between groups at either time point, or within each group between time points ($P>0.05$). CSF tau levels in these neurosurgical patients were similar to those seen in non-neurosurgical patients (2), suggesting that three hours of intracranial neurosurgery itself has no acute effect on AD markers.

Discussion: Our findings are consistent with a recent report that showed no change in Alzheimer's Disease markers until 12-48 hours after anesthesia induction (3). Thus, we are currently measuring these markers at 24 and 48 hours after anesthesia induction. We also discuss our plans to extend these CSF marker studies and correlate them with the occurrence of delirium and postoperative cognitive dysfunction.

References:

1. Planel E, Bretteville A, Liu L, et al. Acceleration and persistence of neurofibrillary pathology in a mouse model of tauopathy following anesthesia. FASEB J. 2009 Aug;23(8):2595-2604.
2. Tang JX, Baranov D, Hammond M, et al. Human Alzheimer and inflammation biomarkers after anesthesia and surgery. Anesthesiology. 2011 Oct;115(4):727-32.

Barking Up the Wrong Tree - Why Anesthetic Mechanism Research Has Failed, and How to Fix It

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How anesthetics prevent consciousness, behavior and memory remain unknown. In 1846 Claude Bernard found anesthetics reversibly block purposeful cytoplasmic streaming inside amoeboid cells. But when Meyer (1897) and Overton (1903) correlated anesthetic action with solubility in a lipid-like, 'hydrophobic' environment (via quantum-level London 'dipole dispersion' forces), anesthetics were assumed to act in lipid membranes on neuronal surfaces, and Claude Bernard's purposeful cytoplasm was forgotten. When Franks and Lieb (1984) found anesthetics act in lipid-like, 'hydrophobic pockets' in proteins, a search began for membrane proteins to account for anesthetic action. Again, Claude Bernard's cytoplasm was forgotten. The search proved fruitless. Eger et al[1] concluded anesthetics must all act on different membrane proteins, or in lipids, again ignoring cytoplasm. Authorities deleted 'loss of consciousness' from the definition of anesthesia[2] (leaving immobility and amnesia, whose mechanisms are also unknown). Mainstream anesthesia research in the early 21st century has no target, and no mechanism. The solution is threefold: 1) Consider consciousness and anesthesia to share a common feature (e.g. London forces). 2) Return to Claude Bernard and anesthetic action in cytoplasm (e.g. dendritic-somatic microtubules). 3) Consider quantum aspects of London forces, in that consciousness may involve quantum biology, e.g. quantum dipoles in microtubules.[3] Tubulin, the component protein of microtubules (and single most prevalent brain protein) binds labeled halothane at one MAC,[4] and proteomic analyses point to tubulin for anesthetic action[5] and post-operative cognitive dysfunction (POCD) [6]. Using computer modeling, we've shown 8 halothane binding sites in intra-tubulin hydrophobic channels suitable for large quantum dipoles. [7] In conclusion, membrane-based anesthetic mechanism research has been barking up the wrong tree. Anesthetics act unitarily by dispersing quantum dipoles in cytoplasmic microtubules.[8,9] 1. Eger et al (2008) A&A 107(3)832, 2. Campana et al (2003) NEJM 348:2110, 3. Hameroff (1998) Phil Trans Roy Soc A 356:1869, 4. Pan et al (2007) J Proteome Res 6(2):582, 5. Pan et al (2008) Proteomics 8(14):2983, 6. Le Freche et al (2012) Anesthesiology 116:779, 7. Craddock et al (2012) PLoS One 7(6) doi:10.1371, 8. Hameroff et al (1982) Physiol. Chem. Physics 14(3):183, 9. Hameroff (2006) Anesthesiology 105:400

Modeling the Ischemic Penumbra in C. Elegans

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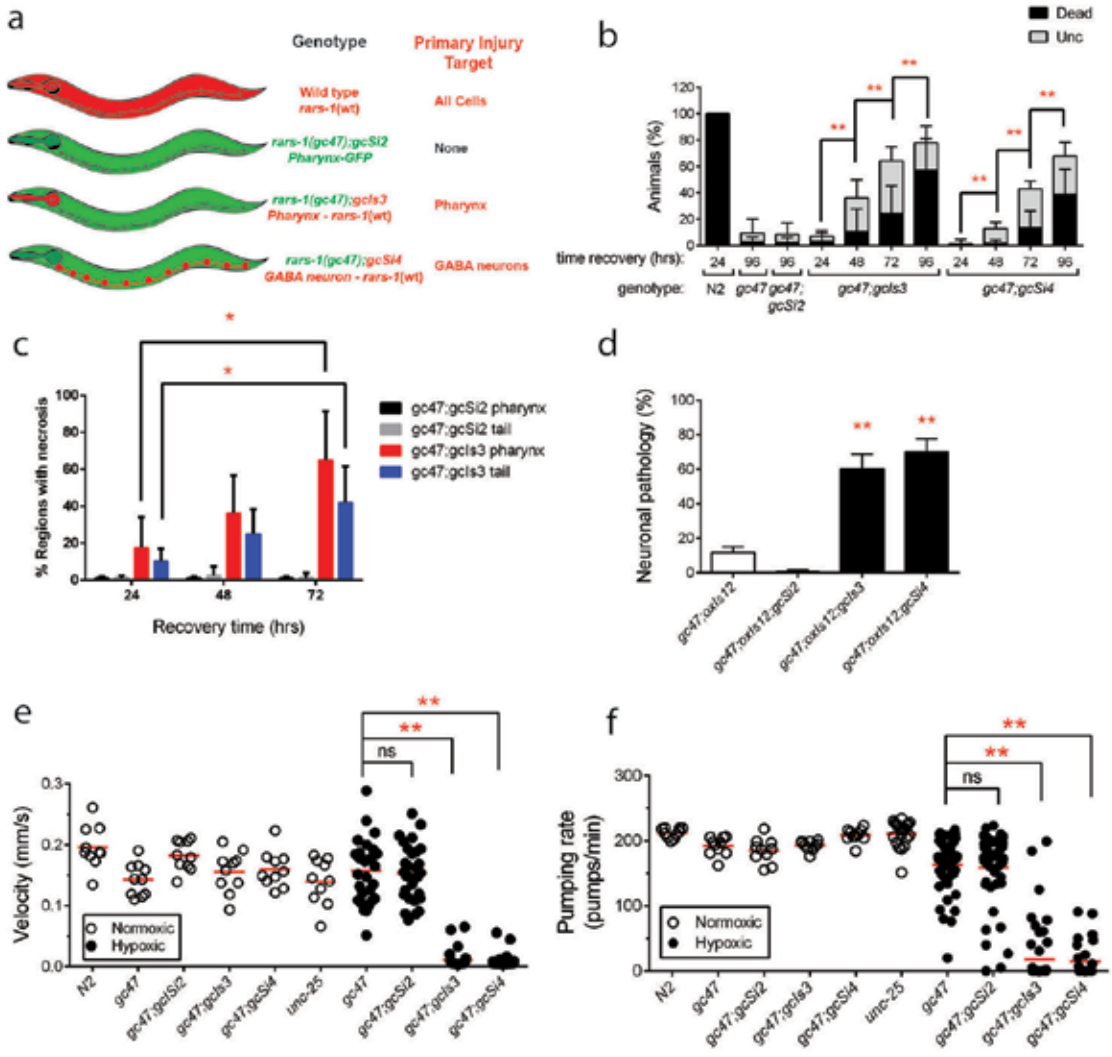
In stroke, neurons in the most severely hypoxic areas die rapidly while those in surrounding less hypoxic areas (termed the ischemic penumbra) may recover or have delayed cell death. The penumbral cells are the therapeutic target in stroke, but a genetically tractable model of the penumbra is lacking. Towards that end, we generated transgenic C. elegans strains where subsets of non-essential cells are made more sensitive to hypoxia than the remaining cells in the organism. The hypothesis is that this will produce animals where localized hypoxic injury will occur and then delayed injury of surrounding cells. We utilized a mutation (gc47) of the translation factor gene rars-1 that confers high level resistance to hypoxia in the nematode C. elegans (1), and into this mutant background, we integrated a transgene expressing wild type rars-1 only in pharyngeal myocytes or GABA neurons (Fig. 1a). After hypoxic incubations, both the pharyngeal myocyte-targeted and GABA neuron-targeted strains initially survive but then have progressive behavioral and cellular defects followed by significant animal death (Fig. 1a-d). Cells died by delayed necrosis (Fig. 1c). Injury and necrosis of non-targeted cells were prevalent as were off-target behavioral defects (Fig. 1c-f, eg. locomotion defects in pharyngeal-targeted or pumping defects in GABA neuron-targeted). We used the pharyngeal myocyte-targeted strain to answer two questions about a previously identified hypoxia resistance mutation (2): First, does the gene act to control non-targeted cell death when the mutation is not expressed in either the targeted or non-targeted cell type? Second, can manipulation of the gene activity only after hypoxic injury reduce delayed cell death? The data show that the answers to both questions are yes (data will be shown at meeting).

Summary: This unique model produces a delayed and secondary hypoxic cell death as is thought to occur in the ischemic penumbra and provides a powerful means to identify factors that ameliorate this type of injury.

Figure 1. Delayed and Secondary hypoxic cell injury/death in C. elegans. Bar graphs are means +/- SD of a minimum of 3 independent trials. ns-non significant,* - $p < 0.05$, ** $p<0.01$, 2-tailed test. a) Schematic of transgenic C. elegans strains generated for this study. b) Time course of onset of uncoordinated movement (Unc) and animal death after hypoxic incubation. c) Time course of appearance of severe necrosis (>5 cells) in either the pharynx or distant tail region. d) Neuronal pathology (axonal beading, breakage, distortion, or cell body loss) in GABA neurons 72 hours after hypoxia in alive animals. e) Velocity of locomotion of alive animals (normoxic or 72 hours after hypoxia), unc-25 is a mutant with no GABA. f) Pharyngeal pumping rate of alive animals (normoxic or 72 hours after hypoxia).

References:

1. Anderson LL, Mao X, Scott BA, Crowder CM. Science 323:630-3, 2009
2. Scott BA, Avidan MS, Crowder CM. Science 296:2388-91, 2002


a
Genotype
Primary Injury Target
Wild type
rars-1(wt)
All Cells
rars-1(gc47);gcSi2
Pharynx-GFP
None
rars-1(gc47);gcIs3
Pharynx - rars-1(wt)
Pharynx
rars-1(gc47);gcSi4
GABA neuron - rars-1(wt)
GABA neurons
b
Dead
Unc
Animals (%)
time recovery (hrs):
genotype:
N2
gc47
gc47; gcSi2
gc47;gcIs3
gc47;gcSi4
c
% Regions with necrosis
gc47;gcSi2 pharynx
gc47;gcSi2 tail
gc47;gcIs3 pharynx
gc47;gcIs3 tail
Recovery time (hrs)
d
Neuronal pathology (%)
gc47;oxIs12
gc47;oxIs12;gcSi2
gc47;oxIs12;gcIs3
gc47;oxIs12;gcSi4
e
Velocity (mm/s)
Normoxic
Hypoxic
ns
f
Pumping rate (pumps/min)
Normoxic
Hypoxic
ns

The Role of Mast Cells in the Pathophysiology of Intracranial Aneurysm

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Unruptured intracranial aneurysms are asymptomatic until they rupture. Clipping or coiling can be offered for the prevention of aneurysmal rupture. Significant technical advancement and refinement have been made in these invasive treatments. However, the mortality and morbidity from clipping and coiling of unruptured aneurysms are not negligible. Therefore, the pharmacological prevention of aneurysmal rupture can be an attractive alternative approach in patients with unruptured aneurysms. Inflammatory cells play key roles in cardiovascular pathologies. Mast cells, classically known as a key regulator of allergic reactions, are recently emerging as integral players in cardiovascular diseases. We hypothesized that mast cells play critical roles in aneurysmal rupture.

1. Pharmacological stabilization of mast cells by cromolyn after aneurysm formation appears to prevent aneurysmal rupture.

As first step, we tested whether mast cell stabilization after aneurysm formation can prevent aneurysmal rupture in a mouse model of intracranial aneurysm. To induce intracranial aneurysms in mice, we combined two well-known factors associated with human intracranial aneurysms—hypertension and disruption of elastic lamina. In C57BL/6J male mice, hypertension was induced by DOCA-salt hypertension (DOCA: deoxycorticosterone acetate). Disruption of elastic lamina was induced by a single injection of elastase (35 milli-units) into the cerebrospinal fluid at the right basal cistern using a stereotaxic method.

In this model, subarachnoid hemorrhage as a result of aneurysmal rupture causes neurological symptoms. And, the neurological symptoms associated with aneurysmal rupture can be easily detected by a simple neurological examination.

We initiated a daily treatment with cromolyn or vehicle six days after aneurysm induction for a total treatment course of three weeks. We used a daily intraperitoneal injection of cromolyn at 25 mg/kg/day. 23 mice received cromolyn, and 14 mice received vehicle.

Although there was no difference in the overall incidence of aneurysms (including both ruptured and unruptured) between the vehicle and cromolyn group ($P = 0.60$), there was a strong trend for the mast cell stabilization to reduce the rupture rate ($P = 0.06$).

2. Genetic deficiency of mast cells appears to reduce aneurysmal rupture.

As a next step, to complement the experiment using the pharmacological stabilization of mast cells, we conducted an experiment using Kit-Wsh mice, mast cell deficient mice. Kit-Wsh mice genetically lack mature mast cells. There was a strong trend for a lower rupture rate in mast cell-deficient mice when compared to wild-type mice, indicating that a lack of mature mast cells prevent aneurysmal rupture ($P = 0.07$). The overall incidence of aneurysms was same between mast cell-deficient mice and wild-type mice.

These results support the hypothesis that mast cell plays a key role in aneurysmal rupture.

Junior Faculty Award

Optogenetic Stimulation of Dopamine Neurons in the Ventral Tegmental Area

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Background: Emergence from general anesthesia is clinically viewed as a passive process dictated by drug clearance. Recent studies demonstrated that methylphenidate (a dopamine reuptake inhibitor) and Chloro-APB (a D1 dopamine receptor agonist) actively induce conscious behaviors in anesthetized rats [1,2], a process that we term “reanimation.” Although dopamine promotes behavioral arousal, the specific dopaminergic neurons that induce it are unknown. The ventral tegmental area (VTA) and substantia nigra (SN) are the two main dopaminergic nuclei in the brain. We recently found that electrical stimulation of the VTA induces reanimation from isoflurane anesthesia, while stimulation of the SN does not [3], suggesting that dopamine release by VTA neurons causes reanimation. However, electrical stimulation does not specifically target dopamine neurons. Optogenetic tools are now available that allow activation of specific neuronal cell types with pulses of light. The current study was performed to test the hypothesis that selective activation of dopamine neurons in the VTA induces reanimation from general anesthesia.

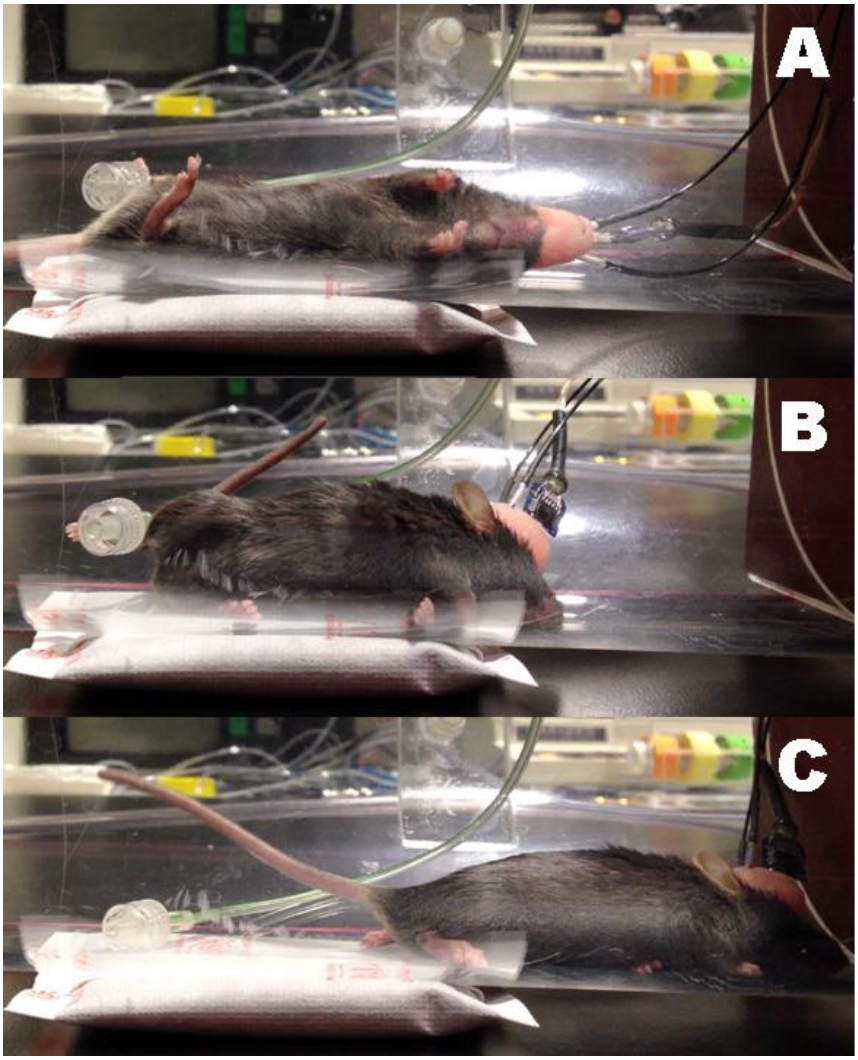
Methods: Genetically modified mice expressing Cre recombinase under the transcriptional control of the dopamine transporter promoter (DAT-cre mice) were used to target dopamine neurons. Anesthetized male DAT-Cre mice were injected with adeno-associated virus carrying FLEX-Channelrhodopsin2 into the VTA or SN, and bilateral fiber-optic cannulas were implanted along with extradural EEG electrodes. The virus causes the expression of Channelrhodopsin2, a light-sensitive ion channel, only in cells that express Cre recombinase. This allows for selective activation of dopamine neurons with pulses of light delivered via the fiberoptic cannulas. After a minimum recovery period of 3 weeks to allow for maximal viral expression, general anesthesia was induced with isoflurane and a dose sufficient to maintain loss of righting with no spontaneous movement was established. During continuous isoflurane anesthesia, optical stimulation of dopamine neurons was initiated using light pulses (480nm, 30mW, 5ms pulses @ 50Hz, 60s on/30s off). After all experiments were completed, histological analysis was performed to confirm the location of the fiber-optic cannulas.

Results: In mice with confirmed fiber-optic cannula placement in the VTA (n=2), light pulses induced arousal and restored the righting reflex during isoflurane anesthesia. Optical stimulation of the VTA also induced a shift in EEG peak power from delta (<4 Hz) to theta (4-8 Hz), indicating arousal. Between stimulation periods, EEG peak power drifted back to delta, and the arousal response waned. In a mouse with the fiber-optic cannula in the SN (n=1), optical stimulation failed to elicit an arousal response during isoflurane anesthesia, and did not induce significant EEG changes.

Conclusions: Dopamine release by VTA neurons induces reanimation from general anesthesia. VTA dopamine neurons represent a novel target to hasten recovery from general anesthesia, and possibly treat emergence-related problems such as cognitive dysfunction.

References:

[1] Solt K, et al. Anesthesiology 2011;115(4):791-803
[2] Taylor NE, et al. Anesthesiology 2013;118(1):30-39
[3] Solt, K, et al. Anesthesiology 2012;117:A543



A. A DAT-CRE mouse under general anesthesia with isoflurane at a dose sufficient to produce loss of righting. The mouse has bilateral fiberoptic cannula aimed at the VTA, where an adeno-associated virus (AAV) vector carrying FLEX-Channelrhodopsin2 was injected and allowed to express for 3 weeks prior to the experiment.

B. Despite continuous general anesthesia with isoflurane, optical stimulation of the VTA with blue light prompted a profound arousal response.

C. Within 10s the mouse has regained the righting reflex, ***while still inhaling isoflurane at the same dose.***

Lidocaine Block of Mutant Rat Skeletal Muscle Na+ Channels Lacking Fast Inactivation: Open Channel Block as a Priming Mechanism for Long-Lived Inactivated Block

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Background: The local anesthetic (LA) lidocaine (LIDO) blocks voltage-gated Na+ channels (NaV) and has concentration- and frequency-dependent clinical utility as a cardiac antiarrythmic (10's μM, ~5Hz) and in nerve conduction blockade in local anesthesia (100's μM, ~100Hz). A key feature of LA action is use-dependent block (UDB) in which repetitive activation produces progressive block (1). QX314, a permanently charged LIDO derivative, produces dual interacting modes of deep-pore, open state block in single NaV channels lacking fast inactivation (2,3) that involves the LA receptor site (3). The study explored for this mechanism in the LIDO pharmacology of NaV lacking fast inactivation and investigated its contribution to LIDO clinical utility.

Methods: Rat skeletal muscle NaV1.4 underwent the triple mutation (I1303,F1304,M1305/Q1303, Q1304,Q1305) to disable fast inactivation (QQQ). Both QQQ and wild type NaV1.4-β1 (WT) where heterologously expressed in Xenopus oocytes. LIDO effects on single-channel and whole-cell currents were studied. Protocols were approved by the IACUC.

Results: LIDO produced dual (discrete and rapid) single-channel, open state block, which was manifest as time-dependent reduction of macroscopic QQQ currents, in accord with a previous model (2) of QX314 dual interacting modes of pore block (DIPB model). LIDO produced QQQ UDB where blocked channels recovered monoexponentially (τ=0.15±0.016s,-100mV) independent of fractional block consistent with gate trapping (4). Fractional block was linearly related (R2=0.99, slope=0.92±0.06) to computed probability (DIPB model) of discrete block (pH-7.4: EC50=368μM,-10mV;EC50=101μM, +30mV). Inclusion of trapping with DIPB model (Trapping DIPB) accounted for single-channel and macroscopic current effects, UDB, and onset and recovery of blocked states. Trapping DIPB model predicts that 25 μm LIDO produces >15% channel block (pH-7.4,+30mV). WT recovery from block induced by short pulses (2ms; τ=0.17±0.016s,-100mV) was similar to QQQ and longer pulses (300ms) slowed recovery by more than two-fold (τ=0.4±0.02s,-100mV).

Summary: The results indicate that LIDO inhibition of QQQ involves DIPB like that of QX314. The results also suggest that trapped pore-blocked channels proceed to long-lived inactivated blocked states in WT. Therefore, LIDO DIPB may lead to long-lived blocked states critical to UDB via two overlapping pathways: 1) LIDO leads to persistent trapped states relevant to nerve conduction block (~100Hz); and 2) trapped pore-blocked states proceed to long-lived inactivated blocked states that contribute in nerve conduction block, but also in anti-arrhythmic therapy with lower activation frequencies . Overall, the findings lead us to propose that LIDO DIPB generally contributes to UDB by priming the LA receptor site prior to transition to long-lived inactivated blocked states.

References:

1) Hille J Gen Phys 69, 1977; 2) Gingrich J Physiol 471, 1993; 3) Kimbrough J Physiol 529, 2000; 4) Starmer et al Biophys J 46, 1984

General Anesthetic Interactions with Beta Tubulin Contributes to the Immobility Endpoint

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Background: Molecular targets of general anesthetics that are both necessary and sufficient to produce any given endpoint have not yet been identified. To begin to do so, we have developed a novel fluorescent general anesthetic, 1-aminoanthracene (1-AMA)(1), which has allowed high-resolution in-vivo imaging of anesthetic distribution (2). In order to achieve molecular resolution, we have more recently developed a photoactive version, 1-azidoanthracene (1-AZA) which is activated by near-UV light to covalently incorporate into its targets. When adducted to a protein, this molecule retains fluorescence and allows identification of both protein targets and their binding sites. Here, we use 1-AZA to achieve in-vivo labeling in transparent organisms, discover its protein targets, and then confirm relevance of these targets through small molecule antagonism.

Methods and Results: Xenopus tadpoles were equilibrated with 1-AZA, exposed to 350 nm light, and then neuronal tissue dissected, solubilized and run on 2D gels. A prominent fluorescence spot was identified as tubulin beta with LC/MS, and MS/MS identified adducted residues as being within the known colchicine binding site (Fig 1). Fluorescence assays with purified tubulin in vitro confirmed binding competition between the anthracenes and colchicine (Fig 2). Polymerization assays of purified tubulin showed significant reduction of Vmax by both 1-AMA and 1-AZA, similar to that of colchicine (Fig 3). In order to confirm that anthracene actions on tubulin contribute to the immobility endpoint seen with these compounds, we pre-incubated tadpoles with epothilone D (epoD), a novel brain-accessible microtubule-stabilizing drug being developed for use in tauopathies (3). EpoD significantly shifted the tadpole immobility EC50 for 1-AMA from 8 mM to 16 mM (Fig 4). It also reduced both the immobility and lethality of 1-AZA after 350 nm exposure.

Discussion and Conclusions: Tubulin has long been proposed as a general anesthetic target, in part because its central role in intracellular dynamics and scaffolding make it highly plausible (4,5). Further, at least four major classes of general anesthetic compounds have been observed to bind specifically to the tubulins – the inhaled anesthetics (6,7), the neurosteroids (8), alkylphenols (unpublished) and the anthracenes (this work). In fact, it was recently shown that the neurosteroids bind essentially the same colchicine sites that we report here (8). It is not yet clear where the clinically used anesthetics (the volatile drugs or the alkylphenols) bind, but it is likely that modulation of microtubule stability in either direction could disrupt cellular functions and signaling sufficiently to cause immobility and unconsciousness. CNS effects of most of the clinically used microtubule targeting drugs (colchicine, taxols) are not prominent, perhaps because they transit the blood brain barrier (BBB) poorly, although it has been reported that colchicine enhances the effects of several anesthetics (9). Perhaps CNS effects will become more apparent with the development of microtubule drugs designed to transit the BBB (such as epoD). In summary, these data indicate that tubulin, an extraordinarily ancient and well-conserved protein, is a direct and contributing target of at least one class of general anesthetic, in part explaining the remarkable conservation of the anesthetic response across biology.

Role of Soluble Epoxide Hydrolase in Exacerbation of Stroke by Type 2 Diabetes Hyperglycemia in Mice

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Hyperglycemia worsens stroke, yet rigorous control in outpatients improved neither incidence nor outcome from stroke (1). Tight glucose control also failed to improve neurologic outcome in critically-ill hyperglycemic patients (2). Attenuating hyperglycemia after stroke onset did not improve neurologic outcome, and may be counterproductive (3). An alternative approach is to interfere with downstream molecular mediator(s) triggered by hyperglycemia but ultimately acting independent of prevailing glycemia. Soluble epoxide hydrolase (sEH), produced by gene EPHX2, is abundant in brain and potential mediator of ischemic injury via removing neuroprotective epoxyeicosatrienoic acids (EETs) (4,5). We previously demonstrated that EPHX2 is overexpressed in type 1 diabetes (T1D), and specific sEH blockade protects brain from the deleterious effect of T1D during stroke. We tested the hypothesis that type 2 diabetes (T2D) hyperglycemia exacerbates cerebral injury (at least partly) by up-regulating EPHX2 mRNA and increasing brain sEH activity in mice. T2D was produced by combined high-fat diet, nicotinamide and streptozotocin in 5-wk old male C57BL/6J mice (6). At 6 wks, T2D and control mice were subjected to 60-min middle cerebral artery occlusion (MCAO) with or without sEH blockade by trans-4-[4-(3-adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid (t-AUCB), 1 mg/kg i.p. x final 6 days before MCAO)(7). Study measures were plasma glucose concentration, EPHX2 mRNA expression, cerebral blood flow, and brain infarct size at 24 hrs. Hyperglycemic T2D mice exhibited 2.8-fold greater EXPH2 expression, and sustained cortical infarct size 40% larger than in controls. Treatment with t-AUCB improved infarct size, and eliminated the difference between T2D and controls. Treatment with t-AUCB moderately decreased glycemic status in T2D but not controls, and augmented post-reperfusion blood flow in T2D but not controls. We conclude that T2D hyperglycemia upregulates EXPH2 mRNA, stimulates sEH production and worsens stroke, an effect obviated by sEH blockade. The protective molecular mechanism(s) may be multifactorial.

1. Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med. 2008;358:2545-59.
2. NICE-SUGAR Study Investigators. N Engl J Med. 2009;360:1283-97.
3. Gray CS, Hildreth AJ, Sandercock PA, et al. (GIST-UK). Lancet Neurol. 2007;6:397-406.
4. Zhang W, Koerner IP, Noppens R, et al. J Cereb Blood Flow Metab. 2007;27:1931-40.
5. Revermann M. Curr Opin Pharmacol. 2010;10:173-8.
6. Nakamura T, Terajima T, Ogata T, et al. Biol Pharm Bull 2006 29:1167-1174
7. Liu JY, Tsai HJ, Hwang SH, et al. Br J Pharmacol. 2009;156:284-96.

Poster Presentations

Education

EDU 16 (2)

Determinants, Associations, and Psychometric Properties of Resident Assessments of Anesthesiologist Operating Room Supervision
Franklin Dexter, M.D., Ph.D.; Bradley Hindman, M.D.; Clarence D. Kreiter, Ph.D.; Ruth E. Wachtel, Ph.D., M.B.A.
University of Iowa

EDU 17 (7)

Simulation-Based Training Induces Cognitive Bias: The Case of a Difficult Airway Curriculum
Christine S. Park, M.D.; Ljuba Stojiljkovic, M.D., Ph.D.[1]; Biljana Milicic, M.D., Ph.D.[2]
Northwestern University, Feinberg School of Medicine[1]; University of Belgrade[2]

EDU 18 (15)

Analysis of Resident Scholarly Activity on Department Cost and Resident Clinical Experience
Tetsuro Sakai, M.D., Ph.D.; Nicholas J. Schott, M.D.; Trent D. Emerick, M.D.; David G. Metro, M.D.
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EDU 19 (23)

Definitive Training for Anesthesiology PGY1 Residents: A Clinical Skills Course
Jane Easdown, M.D.; John T. Algren, M.D.
Vanderbilt University Medical Center

EDU 20 (37)

Creation and Pilot Testing of Serial Web-based Knowledge Examinations for Pediatric Anesthesiology Fellows
Srijaya Reddy, M.D.; Nina Deutsch, M.D.
Children's National Medical Center

EDU 21 (46)

Successful Transition to Anesthesia Residency Training: A Multicenter Study of an Online Distance Learning Program Designed to Prepare Interns for Anesthesia Residency Training
Matthew J. Erlendson, B.A.[1]; Lynn Ngai, B.S.[2]; Monica Garbin, M.A.[3]; Anna Clemenson, B.A.[1]; John Sun, B.S.[1]; Larry F. Chu, M.D.[1]
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EDU 22 (83)

Introducing Fundamentals of Critical Care Support (FCCS) Into the Undergraduate Medical Curriculum – An Innovative Pilot Curriculum Program
Arna Banerjee, M.D.; Matthew B. Weinger, M.D.
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EDU 16 (2)

Determinants, Associations, and Psychometric Properties of Resident Assessments of Anesthesiologist Operating Room Supervision

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University of Iowa

Background: A study by de Oliveira Filho et al. reported a validated set of 9 questions by which Brazilian anesthesia residents assessed faculty supervision in the operating room (Anesth Analg 2008;107:1316-22). The aim of this study was to use this question set to determine if faculty operating room supervision scores were associated with residents' year of clinical anesthesia training and/or number of specific resident-faculty interactions. We also characterized associations between faculty operating room supervision scores and resident assessments of: 1) faculty supervision in non-operating room settings, 2) faculty clinical ability (family choice), and 3) faculty teaching effectiveness. Finally, we characterized the psychometric properties of the de Oliveira Filho question set in an U.S. anesthesia residency program.

Methods: All 39 residents in the Department of Anesthesia of the University of Iowa in their first (n=14), second (n=13), or third (n=12) year of clinical anesthesia training evaluated the supervision provided by all Anesthesia faculty who staffed in at least one of three clinical settings (operating room, [n= 49], surgical intensive care unit [SICU; n=10], Pain Clinic [n=6]). For all resident-faculty pairs, departmental billing data was used to quantitate the number of resident-faculty interactions and the interval between the last interaction and the assessment. A generalizability study was performed to determine the minimum number of resident evaluations needed for high reliability and dependability.

Results: There were no significant associations between faculty mean operating room supervision scores and: 1) resident-faculty patient encounters (Kendall's τ_b=0.01, 95% CI = -0.02 to +0.04, P=0.71), 2) resident-faculty days of interaction (τ_b = -0.01, 95% CI = -0.05 to +0.02, P=0.46), and 3) days since last resident-faculty interaction (τ_b=0.01, 95% CI = -0.02 to 0.05, P=0.49).

Supervision scores for the operating room and SICU were highly correlated (τ_b=0.71, 95% CI=0.63 to 0.78, P<0.0001).

Supervision scores for the operating room were highly correlated with family choice scores (τ_b=0.77, 95% CI=0.70 to 0.84, P<0.0001) and teaching scores (τ_b=0.87, 95% CI=0.82 to 0.92, P<0.0001) (Figure 1).

High reliability and dependability (both G- and phi-coefficients > 0.80) occurred when individual faculty anesthesiologists received assessments from 15 or more different residents.

Conclusion: Supervision scores provided by all residents can be given equal weight when calculating an individual faculty anesthesiologist's mean supervision score. Assessments of supervision, teaching, and quality of clinical care are highly correlated. When the de Oliveira Filho question set is used in a U.S. Anesthesia residency program, supervision scores are highly reliable and dependable when at least 15 residents assess each faculty.

Simulation-Based Training Induces Cognitive Bias: The Case of a Difficult Airway Curriculum

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Background: Cognitive errors interfere with clinical decision-making and can threaten patient safety (1). With the growing use of simulation-based training it is important to understand how this learning affects cognitive processing. In this study, we tested the hypothesis that the design of a simulation-based difficult airway curriculum would induce cognitive bias.

Methods: Twenty-three novice anesthesiology residents were enrolled in this IRB-approved study. All residents received a lecture covering the American Society of Anesthesiologists' Difficult Airway algorithm (2), presenting a sequence of mask ventilation and laryngoscopy, followed by supraglottic airway, with cricothyroidotomy as the last resort. Using a crossover study design, residents were randomized into two groups. One group received practical training in cricothyroidotomy (CRIC Group), while the other received practical training in supraglottic airway placement (SGA Group). After the mid-test, the groups switched. Residents were given a cannot-ventilate, cannot-intubate scenario on the high-fidelity simulator at baseline, mid (at 3 weeks) and final (at 6 weeks). Use of airway maneuvers were documented by blinded review of videotaped performance. Data were analyzed using McNemar and Fisher's exact test for categorical variables. Response times were analyzed using independent samples t-test and RM-ANOVA.

Results: From baseline to mid-test, the SGA Group increased use of supraglottic airway, but not cricothyroidotomy. The CRIC Group increased cricothyroidotomy performance, but not supraglottic airway. After completion of training in both techniques, the SGA Group demonstrated increased both supraglottic airway (P=0.008) and cricothyroidotomy (P=0.008) use. However, the CRIC Group increased cricothyroidotomy use (P=0.008), but failed to change practice in supraglottic airway (P=1.000). An analysis of final test response times showed that the CRIC Group was slower to perform supraglottic airway and faster to perform cricothyroidotomy (P=0.001, Figure 1).

Discussion: Initial practical training in only one technique caused cognitive bias in both groups. The chief finding was an asymmetrical effect of training sequence after completion of training. Initial training in cricothyroidotomy caused cognitive bias that did not correct despite subsequent supraglottic airway training. By contrast, initial training in supraglottic airway resulted in incorporation of both supraglottic airway and cricothyroidotomy. Educators must be alert to designing cognitively informed curricula for learners.

1. Stiegler MP, Neelankavil JP, Canales C, Dhillon A: Cognitive errors detected in anaesthesiology: a literature review and pilot study. Br J Anaesth 2012; 108: 229-35.
2. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 2003; 98: 1269-77.

Analysis of Resident Scholarly Activity on Department Cost and Resident Clinical Experience

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Introduction: Scholarly activity during residency is an important aspect in the academic training of future anesthesiologists. However, residents' scholarly activity has an influence not only on their clinical training but incurs financial obligations to residency training departments. The cost of this equilibrium has yet to be reported. The objective of this study is to analyze anesthesiology department financial commitment and the effect on clinical experience for anesthesiology residents who pursue scholarly activity during their training.

Methods: This IRB exempt study was conducted within a large academic anesthesiology residency program with a total of four graduating classes (2009 through 2012). Data was collected for each resident on months spent for a dedicated resident research rotation (RRR), the number of scholarly projects completed, the number of conferences attended with the dates away from clinical duty, and ACGME case log entries. Comparison was made between residents who did and did not elect a RRR in the numbers of scholarly activity projects, conference attendance, and ACGME cases using Mann-Whitney U test. A p value of less than 0.05 was considered statistically significant. The cost of the department for clinical coverage during residents' research activities was calculated, using an estimated average cost of $675 (range $550 to $800) with the local CRNA pay scales for a 10-hour shift per day.

Results: A total of 68 residents were included in analysis. All residents fulfilled case log numbers and scholarly activity under ACGME requirements. Twenty-four residents (35.3%) completed a RRR with an average duration of 3.7 months. The residents who completed a RRR completed more scholarly projects [5 (4-6.3): median (25%IQR-75%IQR) vs. 2 (0-3): $p<0.0001$], attended more conferences [2 (2-4) vs. 1 (0-2): $p<0.0001$], but had less ACGME cases [904 (768-1037) vs. 1171 (930-1421): $p=0.0021$] compared to those who did not complete a RRR. The overall average cost of the department per resident who fulfilled a RRR was $13,500 (range 11,000 to 17,600) per month, defined as a 50-hour work week and four weeks a month. The average length away from duty for conference attendance by a resident was 3.2±0.2 (mean±SD) days at an average cost to the department at $2,160 (range 1,760 to 2,816) for clinical coverage. The annual average departmental support for residents' travel for conferences was an additional $1,424±133 per trainee based on the conference travel reimbursement data during the study period. Taken together, the estimated cost for the department for resident research activity during their tenure of residency was a median $10,120 (7,420-45,558) per resident.

Conclusions: Residents' scholarly activities require a significant departmental financial support. Residents who elected to spend dedicated research months completed significantly more scholarly projects but experienced less clinical case management opportunities.

EDU 19 (23)

Definitive Training for Anesthesiology PGY1 Residents: A Clinical Skills Course

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Background: PGY1 residents require specific clinical knowledge and skills to manage patients on the front line of hospital practice but do not often receive definitive training to do so. It is essential for resident well-being, self-confidence and patient care to address these needs early in the intern year. This three-week course was created to provide essential skills in perioperative medicine for Anesthesiology residents early in the PGY1 year.

Hypothesis: A clinical skills curriculum for PGY1 residents will increase confidence in skills and patient care in the perioperative setting.

Curriculum Design: The residents met in focus groups with the course director to review a list of proposed educational offerings. Their input assisted to create a curriculum with the topics and skills considered most important for the PGY1 year. In addition, each PGY1 was surveyed to determine his/her existing knowledge, experience and confidence with procedures. The focus groups and survey shaped the development of the subsequent curriculum.

Forty topics were chosen for the course. The course director determined the appropriate instructor and setting for each topic. Instructors included Anesthesiology, Hematology and Radiology faculty members, senior residents, OR and blood bank technicians and PACU nurses. There were two to three educational sessions each day including small group case-based didactic sessions, practice with partial task trainers and high fidelity simulation. The residents assisted in first case starts in the operating room. Each resident was responsible for completing daily readings and participation in discussion. Residents kept a log of procedures and a journal for reflection. The residents contributed to the course development by evaluation of new websites/ podcasts or videos of procedures to create a teaching bank. The course was assessed by a survey completed at a focus group led by the Chief Resident. Residents were assessed by attendance and participation, procedure logs, and self-reported increase in confidence. An informal assessment of progress was made by group viewing and evaluation of a video of their performance during simulation of critical events at the start and end of the course.

Results and Outcome: Fifteen PGY1 residents in groups of five completed this three week perioperative skills course. Preexisting experience and confidence were highest in IV placement and direct laryngoscopy and lowest in use of fiber optic bronchoscopy. Residents requested sessions on ventilator management, ECGs and use of ultrasound. Residents' confidence in performance of procedures, such as placing intravenous or arterial catheters, increased but did not reach statistical significance. However, confidence in knowledge and ability to manage the following clinical situations increased significantly: ability to read a CXR, order PCA, manage ventilator settings, disclose to a patient and manage a critical event on the floor. (Table 1) Evaluations obtained at focus groups were uniformly positive. All participants recommended that this course be repeated for future PGY1 residents. The residents reported as strengths of the course the opportunities to practice skills (IV access, arterial lines, airway management and ultrasound) and use of simulation to consolidate knowledge with skills. Future improvements suggested a dedicated website for dispersal of readings and videos, PowerPoint presentations, and scheduling. A formal assessment of clinical performance with simulation pre and post course is being developed.

Creation and Pilot Testing of Serial Web-based Knowledge Examinations for Pediatric Anesthesiology Fellows

Srijaya Reddy, M.D.; Nina Deutsch, M.D.
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Multiple-choice examinations are designed to assess fund of knowledge and identify areas of weakness. The Anesthesia Knowledge Test (AKT), a series of multiple-choice exams, was developed to assess anesthesia resident knowledge and gauge progressive learning. Administered at intervals, the AKT has been shown to predict which residents will pass the anesthesiology written board examination . Currently, there is no such tool for pediatric anesthesiology fellows (PAFs). Thus, we aimed to create a series of multiple-choice exams to assess fund of knowledge and identify areas of weakness in PAFs over time. Furthermore, we aimed to determine if providing feedback identifying areas of deficiency would result in knowledge gains using pilot testing. We hypothesize that a knowledge assessment tool for PAFs can be developed and that providing keywords for missed question items will result in knowledge gains in subsequent testing.

We developed the Pediatric Anesthesia Comprehension Assessment (PACA) tool: a 150 multiple-choice question database encompassing the major subject areas of pediatric anesthesia. Keywords were generated for each question based on topic. We created 3 different exams to assess PAFs at the 2 (PACA-2), 6 (PACA-6), and 11-month (PACA-11) training intervals. Each 50 question exam was organized based on complexity and depth of knowledge tested such that the degree of difficulty was appropriate for the level of training and targeted a 60% correct response.

We pilot tested the PACA-2 and PACA-6 with 8 PAFs through an internet-based platform. The PACA-2 was administered following completion of 2 months of fellowship. Keywords for the items answered incorrectly were distributed to each respective fellow following testing. The PACA-6 was then administered following completion of 6 months of training. In order to test the impact of providing feedback with keywords, 25 of the most frequently missed questions on PACA-2 were repeated verbatim on the PACA-6. These repeated questions covered the full gamut of the content areas tested. Each PAF served as their own control. We assessed each PAF's performance over time and compared their responses to the repeated questions with paired t-test. Significance was set at .05.

All trainees successfully completed both exams. Testing yielded a mean correct score of 60.3% ± 4.3 with the PACA-2 and 56.8% ± 4.9 with the PACA-6. However, when compared to PACA-2 performance, PAF performance significantly declined on the PACA-6. In contrast, there was a significant increase in correct responses to the 25 repeated questions from 33% ± 9.5 to 45% ± 8.5.

Here we demonstrate that a comprehensive assessment tool can be developed for PAFs. Although the degree of difficulty for both the PACA-2 and PACA-6 was in line with our goal for the tool, relative decreased performance on the PACA-6 likely reflects testing for an increase in knowledge that outpaced actual learning at the 6 month interval. Importantly, interval improvement for repeated items where keywords had been provided, suggests knowledge gains. Thus, with further development, the PACA has the potential to become a fundamental assessment tool in pediatric anesthesiology fellowship education.

Successful Transition to Anesthesia Residency Training: A Multicenter Study of an Online Distance Learning Program Designed to Prepare Interns for Anesthesia Residency Training

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START is an innovative, distance learning online educational program taught during the PGY-1 internship year. It has been shown in a previous single institution study to ease the transition from internship to residency (JGME, in press March 2013). The purpose of this multicenter observational study is to test whether this 10-month program increases anesthesia knowledge, increases interns' self-assessed preparedness to begin anesthesia training, and to determine if these results are generalizable across 4 anesthesia training programs in the United States: Stanford, Yale, Mount Sinai, and UC Davis. START is administered to interns once per month using the Moodle learning management system. Each monthly module is comprised of five components: short video podcasts, longer video lectures, interactive/ collaborative activities, pre- and post-quizzes, and an evaluation/ feedback component. 75 interns participated in the 2011- 2012 START program. 75 interns from the previous year who did not go through START were used as historical controls. A survey assessing preparedness to perform 14 basic anesthesia skills was administered before and after START, utilizing a five-level Likert scale. Assessment in changes in anesthesia-related knowledge are measured with pre- and post- module quizzes. Survey data on subjective feelings of preparedness for residency, stress levels, and connectedness to faculty and institution were further assessed via a five-level Likert scale five months following the 2011-2012 START program. Qualitative analysis was performed using NVivo 10. 37 prior START participants completed the follow up survey. Our results show that the START program improves anesthesia knowledge. Quiz scores on anesthesia knowledge improved significantly when pre-curriculum knowledge assessments were compared with post-curriculum tests. The average learning improvement across all four sites was 34.5% ($p<0.0001$) and was not significantly different between sites (p-value of interaction=0.235). Interns self-assessed feelings of preparedness to begin residency increased on average by 48% after completing the START program ($p<0.0001$). There was a significant difference in the self assessed-preparedness scores compared to controls who did not take the course (20.8 vs. 14.1, <.0001). Qualitative data analysis show that 94.6% of interns answered "agree" or "strongly agree" when asked if they felt more prepared to begin their anesthesia residency after completing START. Between the four institutions, 81% of interns who completed the follow up assessment survey reported that START helped them to feel less stressed about the beginning residency. Qualitative data analysis show that 36 of 37 interns felt more prepared for residency after completing START. When asked if they felt the schools cared more about their education, 91.9% of the residents say "yes".

Introducing Fundamentals of Critical Care Support (FCCS) Into the Undergraduate Medical Curriculum – An Innovative Pilot Curriculum Program

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Introduction: Nineteen percent of questions on USMLE Step II have Critical Care Medicine (CCM) content. Only 45% of US Medical Schools have a CCM curriculum and 60% of these are 4th-year electives. We introduced the Society for Critical Care Medicine (SCCM) sponsored Fundamentals of Critical Care Support (FCCS) into the 3rd-year medical student core curriculum using a weeklong experiential course.

Methods: Retaining the content of the traditional lecture-based FCCS, and with SCCM approval, we created a simulation-based FCCS curriculum. The course was taught every 13 weeks to 24-27 students and consisted of four 2-hour sessions each day for 4 days with 5-8 students per learning group. On the 5th day, each student was paired with a senior anesthesia resident and helped manage a single patient throughout their perioperative course utilizing the skills and knowledge acquired during the week. Three weeks before the course, students were given access to all FCCS lectures through a secure Vanderbilt website, the FCCS textbook and a standard ICU textbook. The FCCS pretest was administered prior to the start of the course and the posttest was administered on Course Day 5. The topics covered and associated FCCS lectures are shown in Table 1. All sessions were debriefed based on the FCCS lecture content. Each course was evaluated using a seven-point Likert scale (1 lowest to 7 highest score; see Table 1). We also administered a standard survey used by the SCCM to evaluate CCM curricula for medical students.

Results: Our first year simulation-based FCCS course involved 104 students. The mannequin and partial-task based sessions received higher scores than the problem-based and Standardized Patient (e.g., Perioperative Risk Assessment) sessions. The average score on the pre-test was 78±15% and on the post-test was 82±7. All of the students passed the FCCS certification exam post-course. Post-course (Table 2), the students were highly favorable; 89% would recommend the course to other students, 88% to other schools, and 87% thought it should be mandatory. Almost a third of students stated that the course had favorably disposed them to consider a career in CCM.

Discussion: FCCS is traditionally a two-day comprehensive (typically weekend) course addressing fundamental management principles for the first 24 hours of critical care. It is targeted to nurses, respiratory therapists, and community physicians to better prepare them to initially manage critically ill patients until transfer or appropriate critical care consultation can be arranged. We believe this is the first incorporation of FCCS into an undergraduate medical curriculum. This is also apparently the first attempt to modify the FCCS curriculum to be more experiential. Students were particularly pleased to receive a clinical certification upon course and test completion. The course appears to have had a favorable influence on some students' career choice. Future directions include sending a follow-up questionnaire to participants to evaluate the course's usefulness in their subsequent clinical endeavors. We also plan to compare medical students' post-course FCCS scores to those of trainees taking the original FCCS course.

Poster Presentations

Compliance/Outreach

CO 23 (5)

Are You Within the Legal Limit? The Anesthesia Consent Process
Sharon Chang, B.A.; Maureen McCunn, M.D.; Rebecca Speck, Ph.D.; Michael Pascarella, D.O, J.D.
Raymond and Ruth Perelman School of Medicine at the University of Pennsylvania

CO 24 (13)

The Impact of Real-Time Automated Paging and E-mail Notifications on Anesthesia Record Documentation
Peter M. Fleischut, M.D.[1,2]; Susan L. Faggiani, RN, B.A., CPHQ[2]; Christian P. Tope, B.S.[2]; Ansara M. Vaz, B.A.[2]; Madhu Mazumdar, Ph.D.[2]; Stavros G. Memtsoudis, M.D., Ph.D.[3]
NewYork-Presbyterian Hospital[1]; Weill Cornell Medical College[2]; Hospital for Special Surgery[3]

CO 25 (38)

What Can We Learn From an Xtreme Dream? The 2012 Diana Nyad Cuba Swim
Gabriel E. Sarah, M.D.[1,2]; William Peruzzi, M.D.[2]; Earl Willis Weyers, M.D.[2]
Jackson Memorial Hospital[1]; University of Miami[2]

CO 26 (50)

International Surgical Missions: More Than Just Operate and Leave
Ram Roth, M.D.; Kris Stensland, B.A.; Tania S. Sierra, M.D.; Elizabeth A. Frost, M.D.
Icahn School of Medicine at Mount Sinai

CO 27 (51)

Are Academic Departments Reverting to Shades of Gray?
Steven D. Boggs, M.D., M.B.A.; Elizabeth Frost, M.D.
Icahn School of Medicine at Mount Sinai

CO 28 (65)

Missing Documentation During Obstetric Anesthesia Procedures Despite an Electronic Medical Record
Luis I. Rodriguez, M.D.; Michael M. Vigoda, M.D., M.B.A.; Vicente Behrens, M.D.
Department of Anesthesia, University of Miami

CO 29 (75)

Comparison of Documented Anesthetic End Times and Claimed Extended Hours
Brian S. Rothman, M.D.; Michael S. Higgins, M.D., M.P.H.
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CO 23 (5)

Are You Within the Legal Limit? The Anesthesia Consent Process

Sharon Chang, B.A.; Maureen McCunn, M.D.; Rebecca Speck, Ph.D.; Michael Pascarella, D.O, J.D.
Raymond and Ruth Perelman School of Medicine at the University of Pennsylvania

Introduction: Informed consent is based upon the right of patient autonomy and is a legal and ethical agreement between physician and patient. Anesthesia consent is often obtained in the immediate pre-operative period, when patients may not be focused on the discussion of the risks, benefits, and alternatives. No studies have studied in depth informed consent discussions in the adult population prior to anesthesia. The goal of this study was to ascertain the practices of anesthesiologists in the consent process. The hypothesis was that physicians with higher levels of training would advise patients of more risks, provide patients with more anesthetic options, and allow the patient more autonomy in deciding the anesthetic plan, though spending less time with the patient.

Methods: In a convenient, consecutive sample of patients, we observed the anesthesia consent process. Outcomes of interest included the risks patients were advised of, number of questions patients asked, and interview duration. The risks identified in the University of Pennsylvania anesthesia informed consent form were those targeted for observation.

Results: 76 unique anesthesia providers (52 residents, 1 fellow, 23 attendings) were observed over a total of 132 pre-anesthetic interviews. 30 physicians were female and 46 male. 54 physicians were white, 17 Asian, 4 African-American, and 1 Latino. Of the 132 patients, the age range was 19-89, with a mean of 54.7 years. 65 patients were female and 67 male. 94 patients were white, 25 African-American, 9 Latino, and 4 Asian. The total duration of the pre-anesthetic interview differed significantly between residents and faculty. The residents spent a mean of 10.5 minutes (628.9 seconds) and attendings spent a mean of 7.9 minutes (471.1 seconds), ($p<0.001$). Of the risks patients were advised of, only tooth damage differed significantly between attending and resident physicians, with residents advising patients of this risk more.

Overall, 69.7% physicians advised patients of the risk of sore throat, 62.1% of nausea and vomiting, 41.7% of tooth damage, 36.36% of heart problems, 18.9% of obstruction of breathing, 18.9% of brain injury (including stroke), 15.9% of death or serious injury, 12.9% of infection, 12.9% of bleeding, 8.3% of nerve injury, 3.0% of blindness, 2.3% of drug reactions during anesthesia, and 2.3% of headache.

12.9% of physicians gave the patient a chance to challenge the established anesthetic plan, while 10.6% gave patients an alternative anesthetic plan (neither differed significantly between residents and attendings). 3.0% told the patient of the risk of not having anesthesia, with only 1.5% offering the alternative of no anesthesia. Only 3.8% of patients read the consent form, beyond just signing. Patients on average held the consent form for 34.6 seconds, including signature time.

Conclusion: Most aspects of the informed consent discussion between anesthesiologists and patients that we observed were not found to significantly differ between attendings and residents. However, many of the requirements of full informed consent, including material risks, benefits, and alternatives, are not being disclosed to patients. This implies an absence of fulfilling the legal definition of informed consent.

CO 24 (13)

The Impact of Real-Time Automated Paging and E-mail Notifications on Anesthesia Record Documentation

Peter M. Fleischut, M.D.[1,2]; Susan L. Faggiani, RN, B.A., CPHQ[2]; Christian P. Tope, B.S.[2]; Ansara M. Vaz, B.A.[2]; Madhu Mazumdar, Ph.D.[2]; Stavros G. Memtsoudis, M.D., Ph.D.[3]
NewYork-Presbyterian Hospital[1]; Weill Cornell Medical College[2]; Hospital for Special Surgery[3]

Background: The incomplete documentation of elements of the anesthesia record is associated with potential loss of revenue, legal liability and consequences related to non-compliance with regulations. Automated, real time alert systems have been shown to improve documentation of procedure related variables.1 However the impact of this technology to improve documentation of electronic signatures, correct attestation of anesthesia care, and accurate documentation of relief times has not been cumulatively studied. Therefore, we sought to investigate the impact of the introduction of a novel, real time alert system on the rates of documentation failures in a large, tertiary care center using automated anesthesia records.

Materials and Methods: The primary outcome of this study was the failure to 1) document an electronic signature, 2) provide a correct attestation, and 3) document attending relief times in a large, tertiary academic center using automated anesthesia records. For this purpose, data on failure rates were prospectively collected 4 weeks prior to the initiation of an automated alert system and compared to rates 4 weeks after implementation. The automated, computer-generated alerts consisted of up to three consecutive pages to the anesthesia provider(s) in case of lack of documentation, followed by an e-mail alert. Omission of documentation within 3 hours of the end of the case was defined as a failure. Failure to document was further analyzed by type of anesthesia provider (i.e. attending, resident or certified registered nurse anesthetist). Rates of failure were computed for each of the 4 weeks prior to and after introduction of the intervention.

Results: In the 8 weeks of the study, a total of 7,105 cases were performed (3,323 pre intervention and 3,783 post intervention). The attestation failure rate was 6.4% (n=214) in the 4 weeks before the alert system was instituted and 0.7% (n=26) thereafter (P=<0.01). In the last week of study, a rate of 0.1% (n=1) was achieved. Similarly, a drop in relief time documentation occurred. Among 255 possible documentation opportunities, 3.1% (n=8) resulted in failure before the intervention, while no omissions among 298 opportunities were recorded thereafter (P=<0.01). E-signature failure rates among attendings, residents and nurse anesthetists before the intervention were 1.9%, 6.9% and 7.5%, respectively. In the following 4 weeks, rates dropped to 0.3%, 0.7% and 0.9%, respectively (P=<0.01). (See Figures 1-3)

Conclusion: The institution of an automated, real time, computerized alert system can significantly reduce the failure rate for anesthesia record documentation related to attestation, relief time entry and electronic signature. Despite the tremendous reduction in failures to document essential elements, further study is needed to identify reasons for remaining failures and discrepancies among the type of anesthesia provider.

1.Ehrenfeld JM, Epstein RH, Bader S, Kheterpal S, Sandberg WS.Automatic notifications mediated by anesthesia information management systems reduce the frequency of prolonged gaps in blood pressure documentation. Anesth Analg. 2011 Aug;113:356-63.

CO 25 (38)

What Can We Learn From an Xtreme Dream? The 2012 Diana Nyad Cuba Swim

Gabriel E. Sarah, M.D.[1,2]; William Peruzzi, M.D.[2]; Earl Willis Weyers, M.D.[2]
Jackson Memorial Hospital[1]; University of Miami[2]

In August of 2012, Diana Nyad, labeled “the toughest athlete in the world,” attempted the record-breaking, 103-mile swim across the Straits of Florida. Diana entered Cuban waters joined by members of various support teams including medical, media, jellyfish surveillance, navigation, shark divers, and coaching.

Diana was joined by two physicians from the University of Miami Department of Anesthesiology who were fully equipped to handle myriad health issues, from minor aches or pains, sprains, fractures or lacerations, respiratory failure, both non-surgical or surgical emergent airway establishment, and complete cardiovascular collapse. Diana would swim in two layered traditional bathing suits during the day and then change to the special “body skin” suit created for protection from jellyfish in the evening. Verbal medical assessments and body temperatures were obtained during each break. Particular attention was paid to responses regarding urine output, shortness of breath, difficulty breathing, and thermal status.

Beyond the incredible physical challenge that this swim presented, our biggest challenge was surprisingly not sharks, but jellyfish. Scientists from the Woods Hole Oceanographic Institution were responsible for underwater filming and surveillance of jellyfish. The team utilized high definition video cameras and infrared monitoring equipment in the water column preceding Diana’s swimming trajectory.

Having been horribly stung in previous attempts, Diana’s level of preparation and prevention included a sophisticated swim skin full body suit and back stroke approach at night as well as the use of novel skin protectants and sting treatments developed by Dr. Angel Yanagihara of the Department of Tropical Medicine at the University of Hawai’i. She anecdotally stated that she had never before seen this many jellies in the Straits. Internationally, biologists have gathered data from various bodies of water and have come to the conclusion that Diana’s observations are correct. The jellyfish population is exploding.

Anesthesiologists treat thousands of individuals at coastal trauma centers and emergency rooms each year. With the rapid explosion of the jellyfish population, hundreds of swimmers could present to these medical settings with symptomatic jellyfish stings with possible progression to cardiovascular collapse. Recent studies show that our currently acceptable treatment guidelines may be causing more harm than good.

The clinical experience gained from this project was immense and it is clear that the anesthesiologist and critical care physician can play an active role in the treatment of extreme athletes both before and after their sporting attempts. With more than 6,500 annual events, open water swimming is a rapidly expanding sport and a cause for concern to the medical community. The number of deaths, accidents or near-fatalities is felt to be on the rise and there is opportunity for our Anesthesiology society to collaborate with coaches, trainers, and teams to improve safety. Very little legislation or medical direction guides athletes during a swim because certified medical personnel do not accompany most swimmers and clinical decisions are largely made by laypersons with variable levels of medical knowledge.

Extra Files:

International Surgical Missions: More Than Just Operate and Leave

Ram Roth, M.D.; Kris Stensland, B.A.; Tania S. Sierra, M.D.; Elizabeth A. Frost, M.D.
Icahn School of Medicine at Mount Sinai

Introduction: Over the past 9 years we have established a relationship between the Icahn School of Medicine at Mount Sinai and a developing world hospital in Honduras. Over this time, we have organized annual surgical missions. Each year new challenges required adjustments. The areas where we made changes have had lasting benefit and might be of value to others who engage in similar missions.

Methods:
1. We developed an intensive medical student and global health curriculum. Students are now intimately involved in the preparation and execution of the program. On average 10 students participate in each mission, alongside 2 resident and 2 attending anesthesiologists. The students promote the relationship with the hospital while the overlapping of 2nd and 4th year students provides continuity for future missions' success.
2. The local reaction to our successful resuscitation of a witnessed cardiac arrest in a post surgical patient made us realize that education, an understanding of a team approach, availability and organization of appropriate drugs were lacking. We shared algorithms, drills and designed a code box to help remedy these deficits. Code boxes are now a standard part of our supplies.
3. As our missions last only one week, postoperative follow up is often difficult. We use cell phone contact from the United States to try to determine outcomes. Surveys made over several years indicate that short term (1 month) contact yields better response rate than long term (1 year).

Results and Discussion:
1. The benefits of surgical missions expand well beyond the patients receiving surgery. Students gain perspective on patient care in resource-poor settings and also take on critical roles in educating local health care providers and in surgical service organization.
2. Identifying and training code team members and developing standardized code supplies and medications have empowered the local staff. A log book to record usage is in place and analyzed annually to determine if other adjustments are necessary.
3. While the response rate for completion of a phone survey at 1 month was about 62%, the number fell to only 8% at 1 year. These response rates may indicate a problem in international service or language barriers. We believe that the quick turnover in cell phone numbers in poor countries may also contribute to the poor response at 1 year follow up. Repeated calling at different times of the day as well as better preoperative patient education, especially in ensuring current phone and family contact information are essential. However, maintaining contact with local staff does provide good follow up information and retains good will.

Conclusion: The benefits of surgical missions expand beyond patients. The opportunity allows for personal growth of all providers. Nevertheless, there is a constant need for adjustments on both sides as we develop the relationship.

CO 27 (51)

Are Academic Departments Reverting to Shades of Gray?

Steven D. Boggs, M.D., M.B.A.; Elizabeth Frost, M.D.
Icahn School of Medicine at Mount Sinai

Introduction: Anesthetic practice and the expectations of the practitioner have changed greatly over the last 30 years. Ambulatory and office practice became the norm, allowing more regulated hours and less or no weekend work. Anesthetic delivery has become much safer, encouraging and even allowing, less experienced professionals to garner a substantial share of the work.

For anesthesiologists who completed residencies 25-30 years ago, private practice was most inviting. Remuneration was excellent, there was little competition, youthful age did not mind long hours, paperwork, rules, regulations, practice parameters, guidelines, administrative protocols were at a minimum. Even the internet was still in its infancy. Today, reimbursement is dwindling, bundled payment is looming large, other groups feel qualified to deliver some degree of anesthesia or analgesia, and our every movement is scrutinized by watchdog groups. Even though children's college tuition and mortgage may have been paid, many would still like to work, albeit in a more protected environment, at lesser salary. But is a return to academic practice feasible or even possible for anesthesiologists after years of private practice?

Method: We sent a short survey to members of the Society of Academic Anesthesia Associations chiefs in the United States (Table 1)

Table 1
1. Have you received applications from private practice anesthesiologists wishing to return to academic practice? Yes / No

2. If so, has there been a recent change in this number of applicants?
- Increase
- No Change
- Decrease

3. Have you hired any of these candidates?
- Number over the past 3 years?
- How many years had/have they been out of academic medicine?
a. < 5 years
b. 5 – 10 years
c. 10 – 15 years
d. > 15 years

4. If you have hired these candidate(s), how successfully have they managed the transition from private practice back into academic practice?
- Extremely well
- Well
- Adequately
- Poorly
- _____

a. Problems that you see that they have had in making the transition (please list):
b. Skills/attributes that they have brought to your department (please list):
c. Reception by existing department members (please list):
d. Have you found it necessary to terminate any of the candidates you hired?

5. How have you handled call responsibilities for these individuals? Any difference from other attendings?

6. If you have not hired these candidates, please describe why they did not meet the needs of your department.

7. Additional comments?

Results: To date, we have received a limited number of responses. The questionnaire was emailed to 411 people. Of those, 159 people opened the link and 28 clicked on survey link.

Of those answering the survey, 100% have received applications from anesthesiologists in private practice. For 80% of these, there has been no change in the number of applicants in the past 5 years, with 20% seeing an increase in applicants from private practice. All respondents have hired a practitioner from private practice. Of these hires, an equal number had been out of academic medicine less than 5 years and between 5 to 10 years. Seventy- five % of academic chairs had hired someone who had been out of academic medicine for more than 10 years.

All respondents said that these hires either performed well or adequately, none were ranked as performing poorly. The skills that these individuals brought to academic practice were good work ethics, insight into billing and collecting, practice management skills and a focus on efficiency and turnover. They were noted to be efficient in their evaluations and were seen as excellent generalists.

Problems identified in practitioners transitioning back into academic medicine were adaptation to a slower schedule and the commonly encountered variable surgical speed. One anesthesiologist was seen as impatient with residents.

Conclusion: We are disappointed at the low return and will resend the survey in hopes of gathering more data. However, it appears anesthesiologists in private practice who desire to return to academic medicine can make the transition successfully. These practitioners bring a different skill set to academic departments, with a focus on productivity, turnover and efficiency – issues which they have encountered in private practice.

Both parties – the applicant and the chair – must examine the reasons motivating the return to academic medicine. The transition can be accomplished, but the practice environment is substantially different, a situation that must be understood and clarified up front to the applicant.

Missing Documentation During Obstetric Anesthesia Procedures Despite an Electronic Medical Record

Luis I. Rodriguez, M.D.; Michael M. Vigoda, M.D., M.B.A.; Vicente Behrens, M.D.
Department of Anesthesia, University of Miami

Introduction: Accurate documentation of every anesthetic encounter is critical for the management and later continuity of care of every patient. Traditionally the anesthetic record is handwritten and studies showing deficiencies in physiologic data suggest that the quality of documentation can be improved.1 Since the implementation of Anesthesia Information Management Systems (AIMS), improvement in quality and timely documentation has been shown,2 with others demonstrating that documentation of other non-physiologic clinical data is often incomplete.3

Methods: We reviewed over 800 anesthetic records from 12/10 to 2/11of pregnant patients admitted for labor and delivery or other pregnancy related procedures that received regional anesthesia: combined spinal-epidural (CSE), epidural (EPI), or spinal (SPI). We looked at three different groups: (1) paper record (PPR) only from Labor and Delivery (L&D); (2) Electronic Medical Record (EMR) only from operating room (OR); and (3) PPR to EMR (L&D to OR). We excluded 14 records in PPR to EMR group where only the EMRs were available. The following non-physiologic clinical data were considered as the minimum requirements for a complete record: IV access and level of placement of neuraxial technique. In case of a CSE or Epidural, we included: loss of resistance (LOR), epidural catheter depth, and epidural catheter removal after delivery or surgery end. We reviewed each record for free text data entry and identified missing data.

Results: We collected a total of 727 patient encounters. The three groups included: 216 PPRs (204 CSE; 11 EPI; 1 SPI); 354 EMRs (279 CSE; 2 EPI; 73 SPI); and 157 PPR to EMRs (145 CSE; 12 EPI). We found that EMRs were more likely to be missing the following items: IV access; level of placement; LOR; and catheter depth. And catheter removal after delivery or surgery ended was more likely to be missing in the PPR to EMR group (Table 1).
EMRs were more likely to have missing documentation than PPRs for: IV access (85/354 vs. 36/216; p=0.046), level of placement (148/354 vs. 18/216; p<0.0001); LOR (18/354 vs. 1/216; p<0.0005); catheter placement (90/354 vs. 5/216; p<0.0001); and catheter removal (42/354 vs. 11/216; p<0.004).

Discussion: Clinicians using EMR are more likely to have incomplete records with missing documentation than those who use paper records, when physicians must entry free text. Modifying the data entry method to predefined menus or drop-down items is an area that requires further research. Whether this is related to documentation of OB anesthesia events or is a more widespread problem will be the subject of our future investigation.

Data in Record	Group of Records	Yes	%	No	%	p Value
IV Access:	Group 1: PPRs	180	83%	36	17%	1 vs 2: p=0.046
	Group 2: EMRs	269	76%	85	24%	1 vs 3: p=0.0037
	Group 3: PPR to EMR	147	94%	10	6%	2 vs 3: p<0.0001
Level of Placement:	Group 1: PPRs	198	92%	18	8%	1 vs 2: p<0.0001
	Group 2: EMRs	206	58%	148	42%	1 vs 3: p=0.1494
	Group 3: PPR to EMR	150	96%	7	4%	2 vs 3: p<0.0001
Loss of Resistance:	Group 1: PPRs	215	100%	1	0%	1 vs 2: p<0.0005
	Group 2: EMRs	263	94%	18	6%	1 vs 3: p=1
	Group 3: PPR to EMR	157	100%	0	0%	2 vs 3: p<0.0005
Epidural Catheter Depth:	Group 1: PPRs	211	98%	5	2%	1 vs 2: p<0.0001
	Group 2: EMRs	191	68%	90	32%	1 vs 3: p=0.0796
	Group 3: PPR to EMR	157	100%	0	0%	2 vs 3: p<0.0001
Catheter Removal:	Group 1: PPRs	205	95%	11	5%	1 vs 2: p<0.0004
	Group 2: EMRs	239	85%	42	15%	1 vs 3: p<0.0001
	Group 3: PPR to EMR	118	75%	39	25%	2 vs 3: p=0.0144

Comparison of Documented Anesthetic End Times and Claimed Extended Hours

Brian S. Rothman, M.D.; Michael S. Higgins, M.D., M.P.H.
Vanderbilt University School of Medicine

Many clinical environments have separate processes for documenting the end time of medical direction in the medical record and the payroll claim of "overtime" or extended hours. We calculated the difference between the latest documented medical direction end time for each provider after 5pm from Vanderbilt's Perioperative Information Management System (VPIMS) and the manually recorded extended hours finish times documented on a separate timesheet that is transcribed into our payroll system. An identical calculation for certified nurse anesthetists' (CRNA) extended hours, where end times represent the time after which they were not physically present performing an anesthetic, was also performed. The mean (standard deviation) for the differences for attending physicians and CRNAs were 18.82 mins (25.17) and 20.32 mins (18.32), respectively.

While there are times when patient care may extend beyond the end time that is necessary and appropriately compensated, a mean difference less than 15 minutes for both groups would have been consistent with the department's expectations. This analysis identified the potential opportunity of approximately $50,000 per year of additional payroll savings assuming a 15 minute additional care time for each provider entry. Using end times automatically generated from the electronic medical record with the payroll system may decrease the mean or standard deviation of differences and possibly lower overtime payroll costs while also ensuring medical staff are not under-compensated due to possible entry errors in the manual overtime payment system. Our work lays the foundation for future efforts examining the effects of automating overtime pay processes, including realizing possible financial savings from a department-wide implementation.

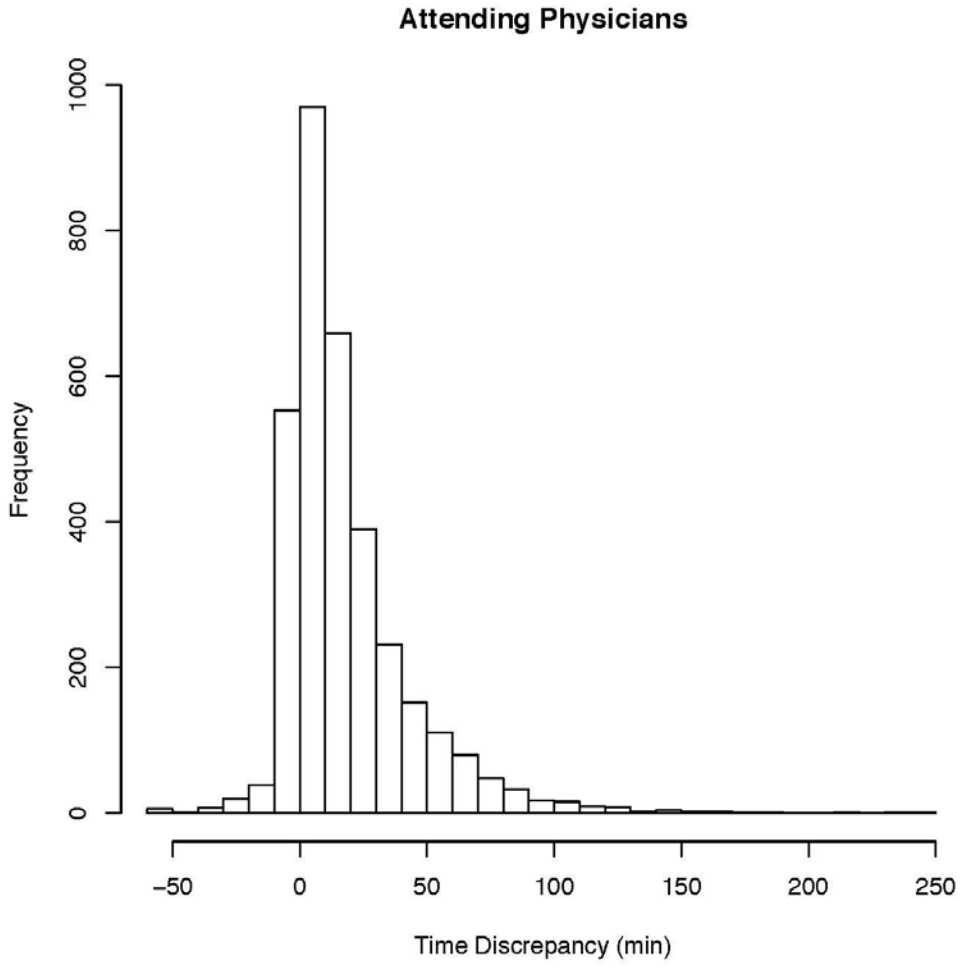

Fig. 1 – Attending physician time differences – The above histogram demonstrates the distribution of the difference between supervision end times and end times reported manually for payroll purposes. Each column represents increments of 10 minutes.

Poster Presentations

Anesthetic Neurotox/Pain

ANP 30 (3)

Isoflurane Overcomes Defective Programmed Cell Death in the Developing Brain of Autistic Mice
Richard J. Levy, M.D.; Ying Cheng, B.S.
Children's National Medical Center

ANP 31 (8)

NOVA1 Variants Regulate RNA Splicing at The Inhibitory Synapse and Persistent Pain Susceptibility
Roy C. Levitt, M.D.[1]; Yan Ping Zhang, M.D.[1]; Shad Smith, Ph.D.[2]; William Maixner, DDO, Ph.D.[2]; Luda Diatchenko, M.D., Ph.D.[2]; Jian Guo Cui, M.D., Ph.D.[1]; Diana Erasso, Ph.D.[1]; Zhiye Zhuang, Ph.D.[1]; Eden Martin, Ph.D.[1]; Susan Slifer, MS[1]; Eugene S. Fu, M.D.
University of Miami[1]; Algynomics[2]

ANP 32 (10)

In Vivo Application of Engineered Receptors for Treatment of Acute and Chronic Pain
Yan Xu, Ph.D.; Yoshika Takahashi, M.D.; Tommy S. Tillman, Ph.D.; Nicole R. Brandon, M.S.; Pei Tang, Ph.D.
University of Pittsburgh School of Medicine

ANP 33 (26)

Interleukin-10 Mediated by HSV Viral Vector Suppressed the Painful Behavior in an HIV-Related Pain Model in Rats - A Preclinical Trial of Gene Therapy on HIV Pain
Shuanglin Hao, Ph.D.; Wan Huang, M.S.; Wenwen Zheng, M.S.; Shue Liu, B.S.; Roy C. Levitt, M.D.; Keith A. Candiotti, M.D.
University of Miami

ANP 34 (28)

Diabetic Neuropathic Pain Development in Type 2 Diabetic Mouse Model and the Prophylactic and Therapeutic Effects of Coenzyme Q10
Keith A. Candiotti, M.D.; Yan Ping Zhang, Ph.D.; Laura Gil, B.A.; Karla Gomez, U.G.; Zhe Yang, M.D., Ph.D.;
University of Miami

ANP 35 (69)

Carbonic Anhydrase 8 (Car8) Deficiency Increases Mechanical and Thermal Hyperalgesia Before and After Carrageenan
Eugene S. Fu, M.D.; Zhiye Zhuang, Ph.D.; Jian G. Cui, M.D., Ph.D.; Diana Erasso, Ph.D.; Roy C. Levitt M.D.
University of Miami Miller School of Medicine

ANP 36 (73)

Factors Associated With the Development of Chronic Pain After Mastectomy Surgery for Breast Cancer
Gildasio S. De Oliveira, Jr., M.D., MSCI; Robert J. McCarthy, Pharm.D.
Northwestern University

ANP 37 (84)

Computational Design of Low Free Energy Hexapeptides for SPAK/OSR1 Binding
Thomas M. Austin, M.D.; Eric Delpire, Ph.D.
Vanderbilt University Medical Center

ANP 38 (11)

Parasagittal Approach During Interlaminal Lumbar Epidural Steroid Injections is Better in Long-Term Pain Relief and Quality of Life Improvement in Patients with Low Back Pain and Unilateral Radicular Pain
Nebojsa Nick Knezevic, M.D., Ph.D.; Kenneth D. Candido, M.D.; Maunak V. Rana, M.D.; Antony Tharian, M.D.; Lalida Chupatanakul, M.D.; Ruben Sauer, M.D.
Anesthesiology Department, Advocate Illinois Masonic Medical Center, Chicago, IL

ANP 39 (12)

Ketamine Neurotoxicity in a Mechanically Ventilated Mouse Pup Model or Not?
Lisa Wise-Faberowski, M.D.; Rani Agarwal, MS; Richard Bland, M.D.
Stanford University; Palo Alto, CA

ANP 40 (40)

Role of Type 1 InsP3 Receptor on General Anesthetic Mediated Synapse and Cognitive Function in Mice
Huafeng Wei, M.D., Ph.D.; Donald J. Joseph, Ph.D.; Mihir Thaker, B.S.; Jacob Boomgaardt, B.S.; Ge Liang, M.D.; Max Kelz, M.D., Ph.D.
Department of Anesthesiology and Critical Care, University of Pennsylvania

ANP 41 (41)

General Anesthesia Causes Disturbances of Mitochondrial Morphogenesis and Synaptic Transmission in Developing Rat Brain
Nadia Lunardi, M.D, Ph.D. [1,2]; Victoria Sanchez, B.S.[1,3]; Annalisa Boscolo, M.D.[4]; Pavle Joksovic, M.D.[5]; Slobodan Todorovic, M.D., Ph.D.[1,3]; Vesna Jevtovic-Todorovic, M.D., Ph.D., M.B.A.[1,3]
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Poster Presentations

Anesthetic Neurotox/Pain *(cont.)*

ANP 42 (49)

Inhibition by Propofol of Respiration by Brain Mitochondria and Cultured Neurons
Gary Fiskum, Ph.D.; Vida Chen, B.S.; Tyler Demarest, M.S.
University of Maryland School of Medicine

ANP 43 (70)

Zero Tolerance for Chronic Pain
Howard B. Gutstein, M.D.; Katherine Barker, Ph.D.; Shanping Shi, B.S.; Miguel Diaz, B.S.; Bing Mo, Ph.D.
MD Anderson Cancer Center

ANP 44 (78)

Effects of Volatile Anesthetics on Neuronal Migration in the Developing Rat Brain
Julie K. Drobish, M.D.; Zoe Gan, B.S., Maryellen F. Eckenhoff, Ph.D.
University of Pennsylvania

Isoflurane Overcomes Defective Programmed Cell Death in the Developing Brain of Autistic Mice

Richard J. Levy, M.D.; Ying Cheng, B.S.
Children's National Medical Center

Introduction: Fragile X Syndrome (FXS) is the leading known genetic cause of autism. The syndrome, caused by a mutation in the Fmr1 gene, silences Fragile X mental retardation protein (FMRP) expression and results in aberrant synapses and excess number of neurons. Defects in programmed cell death (PCD) could impair neuron pruning and developmental apoptosis has been shown to be deficient in Fmr1 mutant drosophila. We hypothesize that PCD is impaired in the developing brain of Fmr1 mutant mice and that anesthetics can overcome such defects. In this work, we assessed the intrinsic apoptosis pathway in the developing brain of two different Fmr1 mutant mouse strains and aimed to determine if isoflurane could therapeutically enhance PCD in these mice.

Methods: The care of the animals in this study was in accordance with NIH and Institutional Animal Care and Use Committee guidelines. We evaluated 10 day old Fmr1 null and Fmr1I304N mutant male mice with appropriate FVB and C57Bl/6 controls on P10. Apoptosis was assessed via immunohistochemistry for activated caspase-3 and TUNEL assays and neuronal quantity determined with cresyl violet staining. Levels of cytochrome c, procaspase-9, APAF-1, Bax, BCL-2, and BCL-xL were measured with immunoblotting. Separate cohorts underwent 1-hour exposure to isoflurane (2%) in air versus air alone on P10. Immunohistochemistry for activated caspase-3 was performed 5 hours post exposure. N=5 per group. Significance was assessed with ANOVA.

Results: 10 day old Fmr1 knockout and Fmr1I304N male mice demonstrated decreased activated caspase-3 and TUNEL positive nuclei in neocortex, hippocampus, and basolateral amygdala and excess number of neurons in primary somatosensory neurocortex and CA3 region of the hippocampus compared to controls. Although both Fmr1 mutant strains demonstrated intact Bax translocation, mitochondrial release of cytochrome c and procaspase-9 was impaired and expression of the anti-apoptotic protein, BCL-xL was increased. Isoflurane exposure increased the number of activated caspase-3 positive cells in neocortex and hippocampus of all animals and restored PCD to control values in Fmr1 mutants.

Discussion: The developing brain of FXS mice demonstrated impaired PCD and excess neurons. Release of pro-apoptotic mediators from mitochondria was impaired in both Fmr1 mutants likely due to increased levels of the anti-apoptotic protein, BCL-xL. Isoflurane, known to decrease BCL-xL and increase cytochrome c release from mitochondria, enhanced apoptosis in the developing forebrain of Fmr1 mutant mice and restored PCD to normal levels. Thus, it is possible that anesthetic agents could overcome defects in PCD to therapeutically enhance neuron pruning and eliminate excess synaptic connections in order to normalize behavior in FXS and autism.

NOVA1 Variants Regulate RNA Splicing at The Inhibitory Synapse and Persistent Pain Susceptibility

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University of Miami[1]; Algynomics[2]

Introduction: Up to 50% of patients who undergo surgical procedures develop persistent post-operative pain. It is now generally accepted that persistent pain development depends on nerve injury and represents a complex heritable trait (influenced by multiple genes). We hypothesize that susceptibility to persistent pain after peripheral nerve injuries are causally associated with variant genes, and that these genes and the pathways can be identified using functional genomics. In this study, we assessed thermal hyperalgesia over time after peripheral nerve injury in mice, and tested the orthologous human candidate gene for association with susceptibility to persistent pain.

Methods: Post-Op Pain Model of Controlled Nerve Injury: 16 genetically diverse inbred strains of mice were characterized after chronic constriction injury of the sciatic nerve (CCI) for withdrawal latency (seconds) to thermal pain (Hargreaves) at Baseline and Days 1, 7, 14, and 21 after CCI. The area under the withdrawal latency response over time, representing the Persistent Pain Index (PPI), was calculated. Mapping PPI loci: Haplotype Association Mapping (HAM) was conducted to identify genome-wide associations between PPI and 7.8 million single nucleotide polymorphisms (SNP) using ANOVA (as implemented by snpBrowser). In this exploratory study, $P<0.001$ was used to select SNPs associated with thermal responses. We next tried to confirm our HAM results using the Efficient Mixed Models Approach (EMMA). Human association was conducted with genomic DNA from patients with chronic pain and disability due to osteoarthritis (OA). Samples were assayed for SNPs in the NOVA1 gene candidate using Illumina 1M-Duo chips. Association was run with PLINK software.

Results: We observed highly significant differences among inbred strains for thermal hyperalgesia after CCI. HAM identified two loci that contribute to the thermal PPI. One was located on chromosome 5 (at 36 - 36.5 Mb) with 4 transcribed annotated candidate genes within the confidence interval. A second was located on chromosome 12 (at 47.75-47.99 Mb) with one transcribed annotated gene called neurooncologic ventral antigen-1 (Nova1), that encodes a neuron-specific RNA-binding-splicing protein which regulates alternative transcript splicing of multiple genes at the inhibitory synapse. EMMA confirms association at both loci ($P<0.00005$). We next tested whether NOVA1 SNPs were associated with persistent OA pain and disability using the validated WOMAC index score in our large OA population (Table 1). These data demonstrate association with NOVA1 SNPs in the 3' region after adjusting for age, gender, race, and multiple tests.

Discussion: Persistent post-op pain is likely influenced by a small number of genes (oligogenic). Nova1 was identified as one of two loci associated with biologic variability in persistent post-op pain. NOVA1 was independently shown to be associated with persistent pain and disability in a large OA population. Based on these data we speculate that NOVA1 functional variants may explain a maladaptive response to nerve injury across multiple levels of anatomic complexity due to altered synaptic functioning affecting pain processing, perception, and higher-level functions associated with persistent pain.

In Vivo Application of Engineered Receptors for Treatment of Acute and Chronic Pain

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University of Pittsburgh School of Medicine

Acute and chronic pain affects more people than cancer, heart disease, and diabetes combined. Treatment options are limited and often involve continuous use of analgesics, which frequently leads to the development of drug tolerance, dependence or abuse. Here we present a new strategy of pain medication by the installation of non-naturally occurring, engineered chloride channel receptors in peripheral nerves so that these nerves can be conditionally hyperpolarized by small molecules that otherwise have no or negligible analgesic effects. The chloride selectivity of the engineered channels and their activation by otherwise non-analgesic primary amines were established by in vitro electrophysiology measurements in oocytes. In vivo expression of the engineered channels in the peripheral nerve endings and dorsal root ganglia in rats was successful and showed no measurable interference with nociception under normal physiological conditions. After the injection of complete Freund's adjuvant (CFA) to induce inflammation in the hind paw, behavioral pain testing showed insignificant differences in pain scores when the engineered channels were not activated. Upon activation, significant alleviation of CFA-induced hyperalgesia and allodynia was observed and quantified. These results demonstrate the clinical potential of a fundamentally different class of therapeutics that are devoid of any centrally acting psychoactive effects and can potentially revolutionize the management of acute and chronic pain. (Funded in part by grants from the NIH, R37GM049202, R01GM056257, and R01GM066358)

Interleukin-10 Mediated by HSV Viral Vector Suppressed the Painful Behavior in an HIV-Related Pain Model in Rats---A Preclinical Trial of Gene Therapy on HIV Pain

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University of Miami

Patients with HIV infection have numerous complications including neurological disorders. HIV-associated sensory neuropathy (HIV-SN) is one of the most common forms of neuropathy, affecting about 30% of adults and children with AIDS. Evidence shows that 30% of these individuals with HIV/AIDS reports pain. HIV-related neuropathic pain is a debilitating chronic condition that is severe and unrelenting. Despite decades of extensive research, the neuropathological mechanisms responsible for the development of this devastating condition of neuropathic pain remain largely unknown. Evidence has demonstrated constitutive overexpression of cytokines and chemokines in the nervous system in HIV patients, and has proposed their roles in HIV infection characterized by inflammation and glia proliferation. We have investigated that HIV viral exterior envelope glycoprotein gp120 applied into sciatic nerve in rats, induces neuropathic pain and increases proinflammatory TNF in the spinal dorsal horn. Here, we report that effects of interleukin-10 (IL-10, an anti-inflammatory cytokines) mediated by herpes simplex virus (HSV) vector on the HIV-related neuropathic pain and the neurochemical changes in the spinal cord and the DRG in the rat model. Recombinant protein gp120 was applied into rat sciatic nerve to induced painful behavior. Mechanical threshold in the hindpaw of rats was tested using Von Fry fibers. Expression of TNF and SDF-1 were tested using western blots and immunofluorescence. We found that IL-10 mediated by HSV significantly suppressed the mechanical allodynia induced by gp120 for a few weeks. IL-10 also reversed the upregulation of TNF and SDF-1 induced by gp120 in the DRG and the spinal dorsal horn at 2 weeks and 4 weeks, but not 7 weeks. The poster will discuss more mechanisms associated to the pain state. The current studies suggest that neuroinflammatory factors are involved in the HIV-related neuropathic pain, and that the results may provide a promising therapeutic approach to relieving HIV-associated pain.

Supported by NIH (S.H.)

Diabetic Neuropathic Pain Development in Type 2 Diabetic Mouse Model and the Prophylactic and Therapeutic Effects of Coenzyme Q10

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University of Miami

Obesity and type 2 diabetes (T2DM) are associated with peripheral neuropathy. We characterized diabetic neuropathic pain (DNP) in New Zealand obese diabetic mice (NZO/HILtJ) as a model of T2DM, and investigated the role of coenzyme Q10 (CoQ10) in the prevention and treatment of DNP. Overexpression of NF-Kb, cytokines (such as CCL2, CXCL10, TLR4) and mitogen-activated protein kinase (MAPK) are considered universal factors contributing to the development of neuropathic pain. The expression of these factors and the inhibitory effects of CoQ10 in the T2DM model were evaluated.

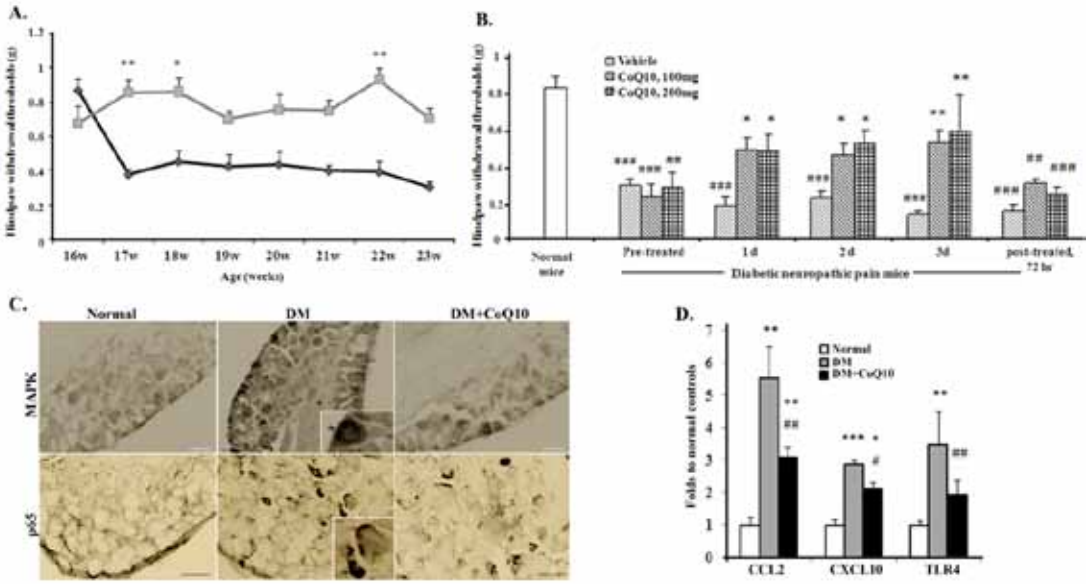
Blood glucose, body weight, and mechanical sensitivity were monitored in mice, age 4 weeks to 24 weeks. Anti-DNP effects of CoQ10 were tested. Oxidative stress and cytokine-related factors expression were evaluated by lipid peroxidation assays, immunohistochemistry, reverse transcription and polymerase chain reaction (RT-PCR).

Mice spontaneously developed T2DM, increased body mass and DNP, indicated by multiple methods. CoQ10 treatment decreased hypersensitivity. Long-term CoQ10 prevented the development of DNP, but did not attenuate diabetes. Blood serum, liver tissue, spinal cord and dorsal root ganglia (DRG) from diabetic mice demonstrated increased lipid peroxidation, which was decreased by CoQ10. The percentage of positive neurons of p65 (the activated marker of NF-KB) and MAPK in DRG were significantly higher in DM mice compared to controls. However, CoQ10 significantly decreased p65 and MAPK positive neurons in the DRG of DM mice. RT-PCR demonstrated that elevated levels of mRNA of CCL2, CXCL10 or TLR4 in the spinal cord in DM mice decreased significantly in CoQ10 treated DM mice.

Conclusion: This model may be useful in understanding the mechanisms of neuropathic pain in T2DM and may facilitate testing of therapies. CoQ10 may decrease oxidative stress in the central and peripheral nervous system by acting as an antioxidant and free-radical scavenger. These results suggest that CoQ10 may be useful in the treatment of DNP.

Figure 1. The prophylactic and analgesic effect of CoQ10 on diabetic neuropathic pain and the inhibition effect to proinflammatory factors.

Figure 1A shows oral daily CoQ10 treatment at a dose of 50 mg/kg/day for 8 weeks (from the age of 16 weeks to 23 weeks) on the development of DM and mechanical allodynia. It demonstrates that CoQ10 treatment effectively inhibited the development of mechanical allodynia (* or ** presents P<0.05 or 0.01 in comparing the data at the same time point in non-CoQ10 and CoQ10 treatment groups). Figure 1B represents reduced thresholds in DM mice pre-treated by CoQ10, indicating neuropathic pain, and CoQ10 treatment significantly reversed the hypersensitivity (### P<0.001, pre-treated or vehicle-treated vs. normal mice; (*P<0.05, **P<0.01 CoQ10 treated vs. pre-treated). Figure 1C shows the immunohistological staining of MAPK and p65 in DRG. The positive neurons in MAPK and p65 increased in DM and CoQ10 treatment decrease the positive neurons. Figure 1D demonstrates the expression of mRNA of CCL2, CXCL10 and TLR4 in the spinal cord by real-time PCR. Again, CoQ10 treatment inhibits the increase of mRNA levels in CCL2, CXCL10 and TLR4 in DM mice (*, ** or *** P<0.05, 0.01 or 0.001 compared to normal controls; # or ## p<0.05 or 0.01 DM vs. DM treated with CoQ10).



Carbonic Anhydrase 8 (Car8) Deficiency Increases Mechanical and Thermal Hyperalgesia Before and After Carrageenan

Eugene S. Fu, M.D.; Zhiye Zhuang, Ph.D.; Jian G. Cui, M.D., Ph.D.; Diana Erasso, Ph.D.; Roy C. Levitt M.D.
University of Miami Miller School of Medicine

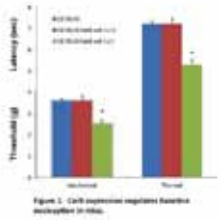
Introduction: Carbonic Anhydrase 8 (Car8) binds to the modulatory domain of inositol 1,4,5-triphosphate (IP3) receptor, type 1 (IP3R1), which is an intracellular IP3-gated Ca2+ channel. Car8 is a naturally occurring allosteric inhibitor of IP3-dependent neuronal excitatory signaling through IP3 receptor 1. IP3 functions as an intracellular second messenger for release of cytosolic free calcium, which serves as a stimulatory signal for diverse calcium-dependent activities such as cellular secretion, contraction, synaptic functioning, and alterations in membrane excitability. Mutation of the Car8 gene produces a functional defect in excitatory transmission to alter synaptogenesis and maintenance of proper synaptic morphology. We present, for the first time, that functional variants of the Car8 gene affect neurobehavioral responses at Baseline and following carrageenan-induced inflammation.

Methods: Three groups of mice were obtained from Jackson Laboratories: 1) C57BLKS wild type (WT) mice that demonstrate no variation in Car8 function; 2) C57BLKS Car8 wdl (+/-) heterozygous mice (heterozygous deletion); and 3) C57BLKS Car8 wdl (-/-) homozygous mice (homozygous deletion). The chemical inflammatory pain model entailed injection of carrageenan into a mouse's left hind paw to induce hypersensitivity. On days 1, 2, and 3 after carrageenan injection, mice were tested for mechanical sensitivity using von Frey filaments in grams and thermal sensitivity using the Hargreaves device to measure response latency in seconds.

Results: As shown in Figure 1, Car8 wdl (-/-) homozygous mice had lower baseline mechanical thresholds and thermal latencies compared to C57BLKS WT and Car8 wdl (+/-) heterozygous mice. The reduced threshold and shortened latency suggest increased pain sensitivity in Car8 wdl (-/-) homozygous mice at baseline. Following carrageenan inflammation, Car8 wdl (-/-)homozygous mice had less mechanical and thermal hypersensitivity compared to C57BLKS WT and Car8 wdl (+/-) heterozygous mice in in the ipsilateral hindpaw. We also found marked reduction in Car8 immunoreactivity in the dorsal root ganglia (DRG) of Car8 wdl (-/-) homozygous mice compared to wild type C57BLKS mice at Baseline. Interestingly, there was greater immunoreactivity of phosphorylated IP3R1 (p-IP3R1) in the DRG of Car8 wdl (-/-) homozygous mice at baseline, suggesting that elevated baseline nociception in Car8 deficient mice may be related to disinhibition of IP3R1 phosphorylation by loss of Car8. We also found that Car8 expression was reduced largely in small neurons in the DRG of C57BLKS WT mice at 6 hours post-carrageenan injection. In contrast, p-IP3R1 expression is present in a few neurons in DRG of WT mice at Baseline. But at 6 hours post carrageenan injection, p-IP3R1 expression is upregulated mainly in small neurons, consistent with the role of Car8 as an inhibitor of IP3R1 phosphorylation.

Discussion: These results suggest that Car8 protein and inhibition of IP3R1 phosphorylation functions in modulating pain. These critical findings teach us for the first time that inactivating DNA variants, or lower levels of functioning Car8 protein, are associated with nociceptor hypersensitivity or enhanced pain in this model system.

Extra Files:



Factors Associated With the Development of Chronic Pain After Mastectomy Surgery for Breast Cancer

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Northwestern University

Introduction: Chronic pain has been shown to affect up to 60% of patients undergoing surgery for breast cancer. Besides younger age, other risk factors for the development of chronic pain have not been consistent in previous studies. The objective of the current investigation was to detect the prevalence and risk factors for the development of chronic pain after breast cancer surgery by examining a patient population from a tertiary cancer center in the United States.

Methods: The study was a prospective observational cohort study. Subjects were evaluated at least 6 months after the surgical procedure. Subjects responded to the modified short form Brief pain inventory and the short form McGill pain questionnaire to identify and characterize pain. Demographic, surgery, cancer treatment and perioperative characteristics were recorded. Propensity matching regression analysis were used to examine risk factors associated with the development of chronic pain.

Results: 300 patients were included in the study. 110 reported the presence of chronic pain. Subjects with chronic pain reported median (IQR) rating of worst pain in the last 24 hours of 4 (2 to 5) and a median (IQR) rating on average pain in the last 24 hours of 3 (1 to 4) on a 0-10 numeric rating scale. Independent risk factors associated with the development of chronic pain were age, OR(95%CI) of 0.95 (0.93 to 0.98) and axillary lymph node dissection, 7.7 (4.3 to 13.9) but not radiation therapy, 1.05(0.56 to 1.95). After propensity matching for confounding covariates, radiation was still not associated with the development of chronic pain.

Conclusions: Chronic pain after mastectomy continues to have a high prevalence in breast cancer patients. Younger age and axillary lymph node dissection but not radiation therapy are risk factors for the development of chronic pain. Preventive strategies to minimize the development of chronic pain are highly desirable.

References:
1)Andersen KG, Kehlet H. J Pain. 2011; 12:725-46

Computational Design of Low Free Energy Hexapeptides for SPAK/OSR1 Binding

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Background: The oxidative-stress-responsive kinase 1 (OSR1) and the STE20/SPS1-related proline/alanine-rich kinase (SPAK) are key enzymes in a signaling cascade regulating the activity of Na+-K+-2Cl- cotransporters (NKCC1-2) and Na+-Cl- cotransporter (1). These cotransporters are involved in pain perception physiology and blood pressure regulation. Both kinases have a conserved carboxyl-terminal (CCT) domain, which recognizes a unique peptide (Arg-Phe-Xaa-Val) motif present in OSR1- and SPAK-activating kinases (with-no-lysine kinase 1 (WNK1) and WNK4) as well as their substrates (NKCC1 and NKCC2) (2). In this study, we utilized the Rosetta Molecular Modeling Software Suite to predict and design hexapeptides that would favorably bind to the CCT domain and compared these decoys to peptide sequences found in nature.

Methods: Starting from a crystal structure of the CCT domain of OSR1 in complex with a hexapeptide (Gly-Arg-Phe-Gln-Val-Thr) derived from WNK4, each amino acid in the hexapeptide was computationally mutated into the other 19 canonical amino acids at all 6 positions using a python script to perform the mutations. Rosetta FlexPepDock, a high-resolution peptide docking (refinement) protocol, was then performed on all 114 mutants with each mutant being docked 1000 times. Total complex energy score and packing energy score was calculated for each run and the scores of the top ten decoys for each mutant were averaged for comparison. In addition, Rosetta Design, a high-resolution design protocol, was also used with FlexPepDock to identify sequences compatible with the CCT domain. 1000 design/docking runs were performed and the top 100 least-energetic decoys were analyzed. The results of these computations were compared to all known protein sequences by searching the NCBI protein database using code written in Visual Basic (Microsoft).

Results: Both methods returned similar results. The Arg, Phe, and Val in positions 2, 3, and 5, respectively, were conserved in the point mutation and design experiments (Figure 1). The Thr in position 6 was mostly recovered in the design (Figure 1) and only 3 of the other amino acids were more energetically favorable in the point mutations. The Gly in position 1 and the Gln in position 4 were replaced by Thr and Asp, respectively (Figure 1). Both of these changes corresponded to lower energy amino acids in the mutations.

Conclusion: Utilizing different applications of the Rosetta Molecular Modeling Software Suite, we found that the Arg-Phe-Xaa-Val motif is indeed critical in binding the CCT domain of SPAK/OSR1. Mutations in the amino acids adjacent to this motif lead to enhanced computational binding, which we will confirm in the laboratory. Also, this will serve as preliminary data as we will computationally screen various small molecule libraries for compounds that interact with the SPAK CCT domain in hopes of later producing novel pharmaceuticals with analgesic and/or antihypertensive properties.

References:

1. Piechotta K, Delpire E (2003) J Biol Chem 278: 52848–52856.
2. Vitari AC et al (2006) Biochem J 397: 223–231.

Parasagittal Approach During Interlaminal Lumbar Epidural Steroid Injections is Better in Long-Term Pain Relief and Quality of Life Improvement in Patients with Low Back Pain and Unilateral Radicular Pain

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Introduction: The purpose of this study was to evaluate the effect of two different approaches (midline and parasagittal) of interlaminar LESI on long-term pain relief and quality of life improvement, and also to assess correlation between pressure paresthesia occurring during the LESI and pain relief.

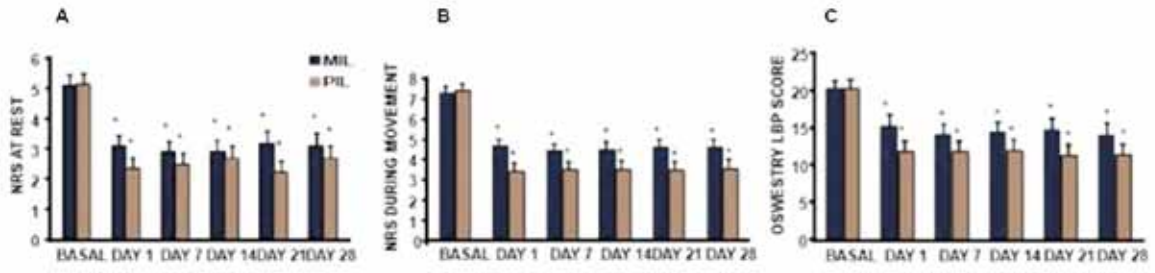
Material and Methods: After IRB approval, 106 patients undergoing LESI for radicular low back pain were randomly assigned to one of two groups (53 patients each) based on approach: midline (MIL) and parasagittal interlaminar (PIL). All patients were followed up for six months. All patients were asked to grade a pressure paresthesia from 0-3 ispilaterally and contralaterally, and confirm whether the pressure paresthesia was in distribution of "usual and customary pain" or distinct from "usual and customary pain". The Oswestry Low Back Pain (OLBP) questionnaire and pain scores at rest and during movement were recording 20 minute before injection and on days 1, 7, 14, 21, 28, 60, 120 and 180 after the injection.

Results: There was no difference between these two groups with respect to age, gender, height, weight or duration of symptoms. Our results showed that single LESI clinically and statistically significantly reduced lumbar radiculopathic pain at rest and during movement (Figure 1a, b). There was also no difference in the basal OLBP score between the PIL and MIL group (20.14±1.33 vs. 20.32±1.04). Both groups showed improvement in the everyday activities and quality of life (Figure 1c).

Patients from PIL group had significantly higher rates of concordant moderate-to-severe pressure paresthesia compared to the MIL group (Figure 1d). The correlation between pain relief and pressure paresthesia was indirect when the paresthesia was identified on the ipsilateral side (concordant) and direct when identified on the contralateral side (discordant) which means that a more severe pressure paresthesia ipsilaterally and a less severe paresthesia contralaterally is related to better pain relief.

After 28 days, we allowed patients to have as many additional LESI as needed. At the six month visit the OLBP score was significantly lower in PIL group (p=0.012) showing better quality of life and everyday functionality than in MIL group. In addition, the patients from midline group received the second LESI at 9.76±.2.03 weeks, and patients from parasagittal group 15.77±2.12 weeks after the first injection (p=0.034).

Conclusion: Both LESI approaches were effective in reducing pain and improving quality of life. However, our study showed that parasagittal approach was more effective in the long-term pain relief and quality of life improvement than the midline approach in patients with unilateral lumbar radiculopathic pain. Furthermore, concordant pressure paresthesia occurring during the LESI could be used as an indicator of proper achievement of medication target, thus increasing the likelihood of an improved outcome toward pain resolution.



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		Midline	Parasagittal	p-value
Pressure Paresthesia	No pressure paresthesia	8 (16%)	6 (12%)	p=0.002
	District from "Usual and customary pain"	19 (38%)	5 (10%)	
	Usual and customary pain	23 (46%)	39 (78%)	
Ipsilateral	No paresthesia	25 (50%)	11 (22%)	p=0.019
	Mild paresthesia	6 (12%)	7 (14%)	
	Moderate paresthesia	13 (26%)	17 (34%)	
	Severe paresthesia	6 (12%)	15 (30%)	
Contralateral	No paresthesia	32 (64%)	45 (90%)	p=0.019
	Mild paresthesia	4 (8%)	2 (4%)	
	Moderate paresthesia	10 (20%)	2 (4%)	
	Severe paresthesia	4 (8%)	1 (2%)	

Ketamine Neurotoxicity in a Mechanically Ventilated Mouse Pup Model or Not?

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Introduction: Anesthetic toxicity in the developing rodent has been demonstrated with several anesthetics, including ketamine (1). Studies of ketamine- induced neurotoxicity in models of developing rodent brain have been without surgical stimulus and mechanical ventilation. We proposed to investigate the effect of surgical stimulus, tracheostomy and mechanical ventilation, in two paradigms of ketamine exposure 8 and 24 hours.

Methods: After Institutional approval and according to NIH guidelines for the humane use and treatment of animals, thirty-two neonatal Balb-C mice (PND4) were randomized into control or ketamine exposure groups. Within each of the two study groups were 16 control animals and 16 ketamine anesthetized animals. The control animals were allowed to spontaneously breathe 40% oxygen for 8 (n=8) or 24 (n=8) hours. The ketamine exposed animals underwent tracheotomy (IM: 60mcg/g bw) and were mechanically ventilated with 40% oxygen for 8(n=8) or 24(n=8) hours. Ketamine (IM; 10 mcg/g bw prn) was administered as needed to approximate 1 MAC anesthesia. The ketamine mice were mechanically ventilated with 40% oxygen (microvent 848; Harvard Apparatus; Holliston, MA) at 180 breaths/min and tidal volumes of 7-8ml/kg for 8 or 24 hours at which time the brains were harvested and placed in 4% paraformaldehyde and paraffin embedded for later H&E and caspase-3 staining (2).

Results: There was no difference in brain injury (H&E and caspase-3) in the 8 hour ketamine exposure group as compared to 8 hour control. Brain injury (H&E and caspase-3) was noted in the 24 hour ketamine exposure group when compared to the 24 hour control. There was no statistical difference in body weight between the 8 and 24 hour control and the 8 and 24 hr ketamine (3.25 +/- 0.66 control;3.32+/-0.49 ketamine) exposure groups. The total amount of ketamine per mouse pup was 0.049 +/-mg/g bw for 8 hour exposure and 0.195 +/- 0.019 mg/g bw. Blood gas analysis in the 8 and 24 hour ketamine groups: pH 7.3 +/- 0.12; PCO2 37 +/- 11.

Discussion: Our study is similar to other rodent studies using volatile anesthesia at 1.0 MAC to prevent movement. In the present study, brain injury is not observed after 8 hours of exposure to ketamine. It is possible that surgical stimulus, tracheostomy, and/or mechanical ventilation attenuated brain injury as a result of ketamine administration. However, this potential protective effect was not observed with a 24 hour exposure to ketamine. It is difficult to determine whether the total dose or duration of ketamine exposure influenced brain injury. Despite this limitation, the study is novel in its use of surgical stimulus and mechanical ventilation in evaluating ketamine neurotoxicity.

References:

1. Liu JR et al. Anesthesiology 2012.117:64-71.
2. Hilgendorff A et al. Am J Physiol Lung Cell Mol Physiol 2011.303:L215-L227.

Role of Type 1 InsP3 Receptor on General Anesthetic Mediated Synapse and Cognitive Function in Mice

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Department of Anesthesiology and Critical Care, University of Pennsylvania

Background: The commonly used general anesthetic isoflurane impairs cognitive function in rodents with unclear mechanisms. We previously demonstrated that isoflurane modulate InsP3 receptor (InsP3R) calcium channels, raising the possibility that overactivation of these channels may contribute to isoflurane mediated effects on neurodegeneration in developing brains and subsequent impairment of cognitive functions. Here, we investigated the electrophysiological and behavioral responses of hemizygous Opistothonos InsP3R type 1 mutant (Opt) and wild type (WT) mice following acute or prolonged isoflurane exposures to gain some insights into the role of these receptors in isoflurane-mediated effects on cognitive functions.

Methods: We employed extracellular field recording to compare the effects of acute isoflurane exposure on the magnitude of long-term potentiation (LTP) and short term plasticity in 4-6 month old hemizygous Opt and WT mice. The loss of righting reflex behavioral test was used to compare the sensitivity of hemizygous Opt and WT mice to isoflurane. Using the same cohorts from the righting reflex experiments, we compared spatial cognitive performance using the Morris water maze (MWM) test. Finally, we used the immunoblotting method to correlate LTP and behavioral data with expression levels of NMDA receptors in hippocampal/cortical lysates.

Results: Hemizygous Opt and WT displayed similar basal synaptic transmission and paired-pulse facilitation. Acute isoflurane exposure did not affect paired pulse facilitation in both hemizygous and WT mice. Hemizygous Opt and WT mice displayed similar levels of Schaeffer collateral CA1 LTP, but differed in their response to the induction and maintenance of LTP in presence of isoflurane. Isoflurane depressed or blocked LTP in WT mice, but had no effects on induction and maintenance of LTP in hemizygous Opt mice. Behavioral analysis of the loss of righting reflex showed that both WT and Hemizygous Opt mice displayed similar induction and emergence curves. However, the isoflurane treated hemizygous Opt mice displayed a transient reference memory impairment compared to treated WT and untreated controls (WT and Opt). Memory retention was significantly improved in isoflurane treated WT mice compared to its controls, but no measureable differences were noted when compared to isoflurane treated hemizygous Opt mice. Finally, hemizygous Opt mice expressed significantly more NMDA receptors at baseline, but repeated isoflurane exposures normalized this difference in NMDA receptor expression.

Conclusion: These results suggest that the type 1 InsP3R plays a critical role in anesthetic-mediated effects on spatial cognition and long-term plasticity.

General Anesthesia Causes Disturbances of Mitochondrial Morphogenesis and Synaptic Transmission in Developing Rat Brain

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Background: General anesthetics cause neurodegeneration in the developing brain via mitochondria-dependent apoptotic cascade. (1) Exposure to anesthesia at the peak of synaptogenesis causes a significant decrease in the number of synapses in rat subiculum. (2) Synaptogenesis relies on proper mitochondrial function and morphogenesis which suggests that mitochondria could be an important target for anesthesia-induced impairment of synaptic function and neuronal development.

Methods: Rats were exposed to midazolam, nitrous oxide and isoflurane for 6-hours on postnatal day (PND 7). The long-term effects of this anesthesia cocktail synaptic transmission and on the morphology and subcellular distribution of mitochondria were examined in subiculum two weeks after the exposure (PND 21).

Results: Upon ultrastructural examination we noted that the experimental mitochondria underwent two stages of degeneration. An early stage was marked by a dilation of cristae and swelling which gave them enlarged appearance compared to controls. In the late stage, mitochondria appeared dark and condensed. The morphometric analysis of the soma of pyramidal neurons revealed that the experimental mitochondria occupied twice as much cytoplasmic area as the controls (22.5 ± 3.1% vs 13.4 ± 1.2%, P<0.05). Large mitochondria (0.26-0.65 μm2) constituted only 5% of total mitochondria in control animals, whereas more than 15% of the experimental mitochondria were in the large category. The morphometric analysis of the presynaptic neuronal profiles revealed that the experimental mitochondria were on average 38% larger than control ones (P<0.05), resulting in a decreased density of mitochondrial profiles in the proximity of newly developing synapse (P<0.05) where their presence is strategically most important. Electrophysiology studies revealed a 49% decrease in net charge transfer of inhibitory postsynaptic currents (P<0.05), a decreased decay time constant from 58 ± 9 ms to 34 ± 4 ms (P<0.05) and a significantly altered paired pulse ratio (P2/P1) from 0.81 ± 0.02 to 0.87 ± 0.01 (P<0.05) in the experimental animals.(3) These functional findings suggest that both postsynaptic and presynaptic mechanisms contributed to decreased synaptic strength of the inhibitory transmission in the experimental group.

Conclusions: Early exposure to general anesthetics causes long-term impairment of mitochondrial morphogenesis and functional integrity leading to the impairment of synaptic transmission in the developing rat brain. Mitochondria appear to be an important intracellular target in anesthesia-induced developmental neurodegeneration.

1. Jevtovic-Todorovic V et al. J Neurosci 2003; 23:876-82.
2. Lunardi N et al. Neurotox Res 2010; 17:179-88.
3. Sanchez V et al. Anesthesiology 2011; 115:992-1002.

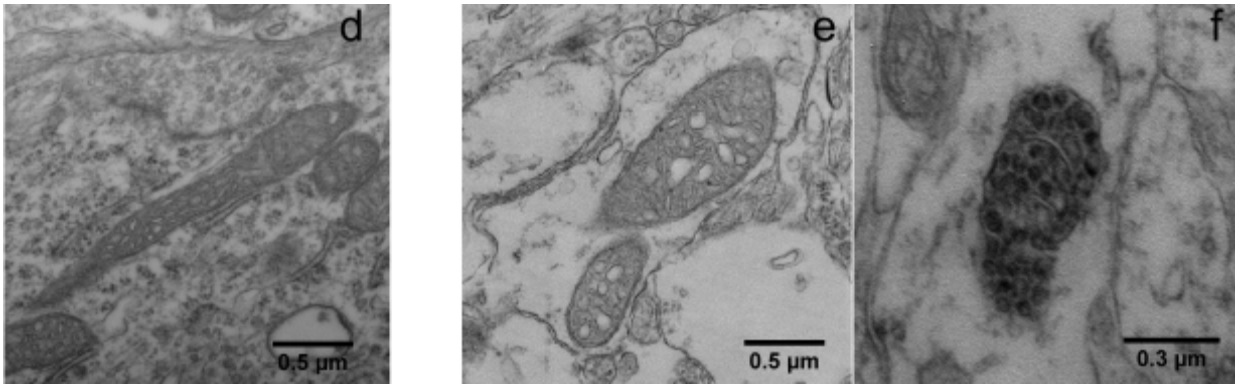

Figure 1: Ultrastructural changes indicative of mitochondria degeneration. Panel d shows a control subiculum. Panels e and f show experimental subiculum. Panel e: mitochondria appeared swollen, with balloon-like cristae, but normal-looking inner and outer membranes (early stage of degeneration). Panel f: dark, condensed and shrunken mitochondrial profiles having no clear outline between the inner and outer membrane (late stage of degeneration).

Inhibition by Propofol of Respiration by Brain Mitochondria and Cultured Neurons

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Background: Propofol can be neurotoxic under some conditions and particularly in the immature brain. One possible mechanism of toxicity is inhibition of mitochondrial respiration and ATP generation. This inhibition was suggested by a decrease in mitochondrial membrane potential observed by in vitro exposure of presynaptic nerve endings to propofol. Direct effects of propofol on oxygen consumption by brain mitochondria or cultured neurons have not been reported. We tested the hypothesis that propofol exhibits dose-dependent inhibition of respiration by isolated brain mitochondria and by primary cultures of immature and mature rat cortical neurons.

Methods: Respiration by synaptic plus non-synaptic mitochondria isolated from the brains of adult rats was measured with an oxygen electrode apparatus in media containing pyruvate plus malate as oxidizable substrates. Maximal Oxygen consumption rates (OCR) by day in vitro (DIV) 12 and 4 rat cortical neurons after 1.5 – 6.5 hr exposure to 10 – 1000 μM propofol were measured using the Seahorse Bioscience XF24 cell respirometer in artificial CSF containing glucose plus pyruvate.

Results: Propofol significantly inhibited adenosine diphosphate (ADP)-stimulated mitochondrial respiration at concentrations of 50 μM (25%) and 100 μM (69%). This inhibition was largely eliminated by 10 mg/ml bovine serum albumin, which binds many different hydrophobic compounds. Exposure of either DIV4 or DIV12 neurons to propofol at 10 to 1,000 μM for 1.5 hr had no effect on OCR. In contrast, exposure to propofol for 6.5 hr resulted in partial inhibition at 250 μM and complete inhibition at 500-1000 μM propofol; however, this inhibition was the result of massive cell death.

Conclusions: Propofol does not inhibit respiration by mature or immature cultured neurons at any anesthesia-relevant concentrations and only inhibits at levels (≥250 μM) that cause acute cell death. Bovine serum albumin protects against inhibition of respiration by isolated mitochondria at 50 – 100 μM propofol, indicating that mitochondria are resistant to inhibition when other hydrophobic macromolecules, e.g., those present in cells, are present. These results do not support the hypothesis that propofol directly inhibits oxidative phosphorylation at anesthesia-relevant concentrations. Any toxic effects of propofol at the mitochondrial level are more likely to be mediated by changes in the activities of pro- or anti-apoptotic proteins.

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ANP 43 (70)

Zero Tolerance for Chronic Pain

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For centuries, opioid drugs such as morphine have been the first-line treatment for chronic pain. However, over time tolerance to opioid analgesia develops, leaving few treatment options and leading to tremendous suffering for pain patients1. Here we show that platelet-derived growth factor receptor beta (PDGFR-β)-mediated signaling is sufficient to cause morphine tolerance and necessary for its behavioral expression. We found that morphine activated PDGFR-β in vitro and in vivo2. Behavioral studies showed that the clinically used PDGFR inhibitor imatinib completely eliminated and reversed morphine tolerance. If imatinib was subsequently discontinued, animals reverted to the tolerant state. Also, administration of the PDGFR-b agonist platelet-derived growth factor BB (PDGF-BB) rendered animals tolerant to subsequent morphine doses. Neither imatinib nor PDGF-BB affected tolerance development to the analgesic drug clonidine, an a-2 adrenoreceptor agonist, suggesting that tolerance modulation by PDGFR-β was opioid-specific. Our results identify a specific cellular signal that selectively mediates morphine tolerance. Furthermore, imatinib is widely used to treat leukemia and gastrointestinal tumors, and clinically well-tolerated. This suggests that our findings could be rapidly translated into clinical practice, potentially reducing the tremendous suffering endured by patients in chronic pain.

Effects of Volatile Anesthetics on Neuronal Migration in the Developing Rat Brain

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Background: Brain development involves a sequence of events including proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis.1 Volatile anesthetics can cause neuronal and glial toxicity, including apoptosis and defects in learning and memory.2,3,4 These toxic effects could be due to disruption of any of the above developmental processes; however, the mechanisms by which anesthetics cause neurotoxicity are not entirely known. In particular, the effects of volatile anesthetics on glial cells and neuronal migration have not been characterized in vivo.

Hypothesis: Volatile anesthetic exposure during early brain development disrupts the function of radial glial cells in the hippocampus, altering neuronal migration and ultimately the final position of neurons in the hippocampus.

Methods: Postnatal day 1 (P1) rats were injected with bromodeoxyuridine (BrdU) in order to label cells that were formed on day P1. These rats were then exposed to volatile anesthetics (isoflurane (1.5%), sevoflurane (2.5%), or desflurane (7%)) for 2 hours or to room air as a control on postnatal day 2. The animals were sacrificed at two different time points: day 7 and day 14. The brains were fixed, embedded in paraffin, and sectioned into 8 um coronal slices. Various immunohistochemical assays were performed, including BrdU (for cells formed on day P1), NeuN (for neurons), and GFAP (for glia), in order to determine the fate of the BrdU labeled cells after exposure to anesthesia. Fluorescent microscopy was used to quantify BrdU labeled cells in the layers of the hippocampal dentate gyrus and to determine any differences between anesthetics and controls on neuronal migration.

Results and Conclusions: In this ongoing study, there is a trend towards fewer total BrdU positive cells in anesthetized rats compared to controls, and this difference is most notable in the number of cells seen in the inner granular layer of the hippocampal dentate gyrus. Additional analysis is currently being performed to determine any further differences between anesthetics, as well as statistical significance.

References:

1. Rice and Barrone (2000) Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environmaltal health prospectives 108:511-533.
2. Jevtovic-Todorovic V, et al. (2003) Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci. 23:876-882.
3. Lunardi N, et al. (2011) Isoflurane impairs immature astroglia development in vitro: the role of actin cytoskeleton. J Neuropathol Exp Neurol. 70:281-291.
4. Stratmann G, et al. (2009) Isoflurane differentially affects neurogenesis and long-term neurocognitive function in 60-day-old and 7-day-old rats. Anesthesiology 110:834-848.

Poster Presentations

Anesthetic Delivery-Monitoring/Outcomes

ADM-O 45 (6)

Effects of Multisensory Training on Pitch Perception of a Pulse Oximeter
Joseph J. Schlesinger, M.D.; Joseph Schlesinger, M.D.; Ryan Stevenson, Ph.D.; Mark Wallace, Ph.D.
Vanderbilt University Medical Center

ADM-O 46 (19)

CW 1759-50 An Ultra-Short Acting Nondepolarizer Immediately Antagonized at Any Time by L-Cysteine
John J. Savarese, M.D.[1]; Hiroshi Sunaga, M.D.[1]; Matthew R. Belmont, M.D.[1]; Matthew Murrell, M.D., Ph.D.[1]; Paul M. Heerdt, M.D., Ph.D.[1]; Jeff McGilvra, Ph.D.[2]
Weill Cornell Medical College - New York Presbyterian Hospital[1]; Cedarburg Pharmaceuticals[2]

ADM-O 47 (21)

Drug Infusion System Manifold Dead-Volume Impacts the Delivery Response Time to Changes in Infused Medication Doses In Vitro and Also In Vivo in Anesthetized Swine
Robert A. Peterfreund, M.D., Ph.D.[1]; Mark A. Lovich, M.D., Ph.D.[2]; Matthew G. Wakim, B.S.[3]; Abraham Wei, B.S.[2]; Michael J. Parker, M.D.[4]
Massachusetts General Hospital[1]; Steward St. Elizabeth Hospital, Boston[2]; Tufts UNiversity School of Medicine[3]; Harvard Medical School[4]

ADM-O 48 (39)

Hypobaric Oxygenation During Cardiopulmonary Bypass Eliminates Gaseous Microemboli and Reduces Microvascular Injury in Swine
Keith E. Gipson, M.D., Ph.D. [1]; Robert B. Schonberger, M.D., M.A.[2]; Jeffrey B. Gross, M.D.[1]
University of Connecticut[1]; Yale University[2]

ADM-O 49 (42)

Complications of Continuous Intrathecal Catheters in Obstetric Patients
Daria M. Moaveni, B.S., M.D.; Mohammed A. Abdel Rahim, M.D.; J. Sudharma Ranasinghe, M.D.; Jennifer H. Cohn, M.D.
Department of Anesthesiology, University of Miami Miller School of Medicine - Jackson Memorial Hospital, Miami FL

ADM-O 50 (45)

Development of Stable Volatile Anesthetic Nano-Emulsions for Intravenous Injection at Sub-Anesthetic Concentrations: Preliminary Investigations
Kyota Fukazawa, M.D.[1]; Antonello Pileggi, M.D., Ph.D.[2]; Christopher Fraker, Ph.D.[2]; Camillo Ricordi, M.D.[2]; Ernesto A. Pretto, Jr., M.D., M.P.H.[1]
University of Miami Miller School of Medicine[1]; Diabetes Research Institute, University of Miami[2]

ADM-O 51 (61)

Controlling Anesthetic Vapor Concentration Using Temperature Regulation
Katie J. Schenning, M.D., M.P.H.; Henry Casson, M.D.; Nabil J. Alkayed, M.D., Ph.D.; Michael P. Hutchens, M.D., M.A.
Oregon Health & Science University

ADM-O 52 (67)

A Psychoacoustic Analysis of Alarm Sounds and Perceived Urgency
Richard McNeer, M.D., Ph.D.; Christopher Bennett, Ph.D.; Colby Leider, Ph.D.
University of Miami Miller School of Medicine

ADM-O 53 (20)

Percutaneous Fiber Optic Monitoring for Spinal Cord Ischemia
Angela D'Souza, M.S., BME[1]; Rickson Mesquita, Ph.D.[2]; Thomas V. Bilfinger, M.D.[1]; Robert M. Galler, D.O.[1]; Arjun Yodh, Ph.D.[2]; Thomas F. Floyd, M.D.[1]
Stony Brook University[1]; University of Pennsylvania[2]

ADM-O 54 (33)

Early Potential Biomarker Changes in the Nitric Oxide Pathway in the Exhaled Breath Condensate of Ventilated Respiratory Disease-Free Surgical Patients
Ana Fernandez-Bustamante, M.D., Ph.D.[1]; Jelena Klawitter, Ph.D.[1]; Serpil Erzurum, M.D.[2]; Uwe Christians, M.D., Ph.D.[1]; John E. Repine, M.D.[1]; Tamas Seres, M.D.[1]
University of Colorado[1]; The Cleveland Clinic Foundation[2]

ADM-O 55 (43)

Hemodynamic Collapse Following Pericardiectomy During Emergency Pulmonary Embolectomy
Susan S. Eagle, M.D.; Jeremy M. Bennett, M.D.; Rashid Ahmad, M.D.; Jesse M. Ehrenfeld, M.D., M.P.H.
Vanderbilt University

ADM-O 56 (52)

Patient Selection for Outpatient Surgery: Identifying Those at High Risk for Major Complications
Michael R. Mathis, M.D.[1]; Sachin Kheterpal, M.D., M.B.A.[1]; Norah N. Naughton, M.D., M.B.A.[1]; Amy M. Shanks, M.S.[1]; Robert E. Freundlich, M.D., M.S.[1]; Christopher J. Pannucci, M.D., M.S.[2]
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Poster Presentations

Anesthetic Delivery-Monitoring/Outcomes *(cont.)*

ADM-O 57 (64)

Relationship Between Endogenous Opioid Function and Opioid-Related Side Effects

Rajnish K. Gupta, M.D.[1]; Stephen Bruehl, Ph.D.[1]; John W. Burns, Ph.D.[2]; Asokumar Buvanendran, M.D.[2]; Melissa Chont, MLAS[1]; Ellen Kinner, B.A.[1]
Vanderbilt University School of Medicine[1]; Rush University Medical Center[2]

ADM-O 58 (76)

High-Sensitivity Cardiac Troponin T in Prediction and Diagnosis of Myocardial Infarction and Long-Term Mortality After Non-Cardiac Surgery

Peter Nagele, M.D., M.Sc.[1]; Frank Brown, B.Sc.[1]; J. Philipp Miller[1]; Allan S. Jaffe, M.D.[2]; Fred S. Apple, Ph.D.[3]; Mitch G. Scott, Ph.D.[1]
Washington University[1]; Mayo Clinic[2]; University of Minnesota[3]

ADM-O 59 (77)

The Use of Preoperative Resources in Low Risk Patients Older Than 65 Years

Stephan R. Thilen, M.D., M.S.; Miriam M. Treggiari, M.D., M.P.H., Ph.D.; Edward M. Weaver, M.D., M.P.H.
University of Washington, Seattle, WA

ADM-O 60 (79)

Do Anesthesiologists Matter? Assessing the Variation in Surgical Outcomes Due to Anesthesiologists

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University of Michigan Medical School[1]; University of Michigan School of Public Health[2]

Effects of Multisensory Training on Pitch Perception of a Pulse Oximeter

Joseph J. Schlesinger, M.D.; Joseph Schlesinger, M.D.; Ryan Stevenson, Ph.D.; Mark Wallace, Ph.D.
Vanderbilt University Medical Center

Background: The pulse oximeter is a critical monitor in anesthesia practice that has improved patient safety greatly. However, attention to the monitor is compromised by noise and other competing factors. Most negative patient outcomes in anesthesia result from a series of small errors, and as such, improving anesthesiologists' performance with pulse oximetry may translate into improved patient outcomes. Here, we aimed to improve the ability of anesthesiologists to monitor arterial oxygen saturation via pulse oximetry through a multisensory (i.e., audiovisual) training process.

Methods: Fifteen residents' abilities to detect auditory changes in pulse oximetry were measured before and after a multisensory perceptual-training paradigm. Accuracy and response times in detecting changes on the monitor were measured under three levels of attentional load and with and without operating room background noise. The only post-training assessment occurred less than 48 hours after training.

Results: In the condition most similar to operating room (noisy and attentionally demanding), anesthesiology residents showed an average 9% increase in accuracy of pulse oximetry pitch change detection and 7% decrease in response times following training. Fourteen of fifteen residents improved in their multisensory perceptual ability after training.

Conclusions: Multisensory training represents a novel means to improve the performance of detecting changes in the pulse oximeter. Increasing the performance of anesthesiologists has the ability to greatly improve patient monitoring and outcomes by preventing small errors; errors that have the potential to cascade into adverse outcomes. Our work builds a foundation for examining patient outcomes as related to anesthesia education and training

References:

Gaba DM, Lee T. Measuring the workload of the anesthesiologist. Anesth Analg 1990; 71:354-361
Loeb RG. Monitor surveillance and vigilance of anesthesia residents. Anesthesiology 1994; 80:527-533
Stein BE. The Merging of the Senses. MIT Press, Cambridge, MA, 1993
Powers AR, Hillock AR, Wallace MT. Perceptual training narrows the temporal window of multisensory binding. J Neurosci 2009; 29:12265-12274

Figure Captions

Figure1. Accuracy levels for the auditory pulse oximetry pitch detection task. Error bars represent standard error, * indicates $p < 0.05$, and ¥ indicates $p < 0.15$.

Figure 2. Response times for the auditory pulse oximetry pitch detection task. Error bars represent standard error, * indicates $p < 0.05$, and ¥ indicates $p < 0.15$.

Figure 3. Multisensory temporal binding changes with training. * indicates $p < 0.05$. All data points in Panel A are significant at = 0.05 outside of ±20 ms.

Figure 1.

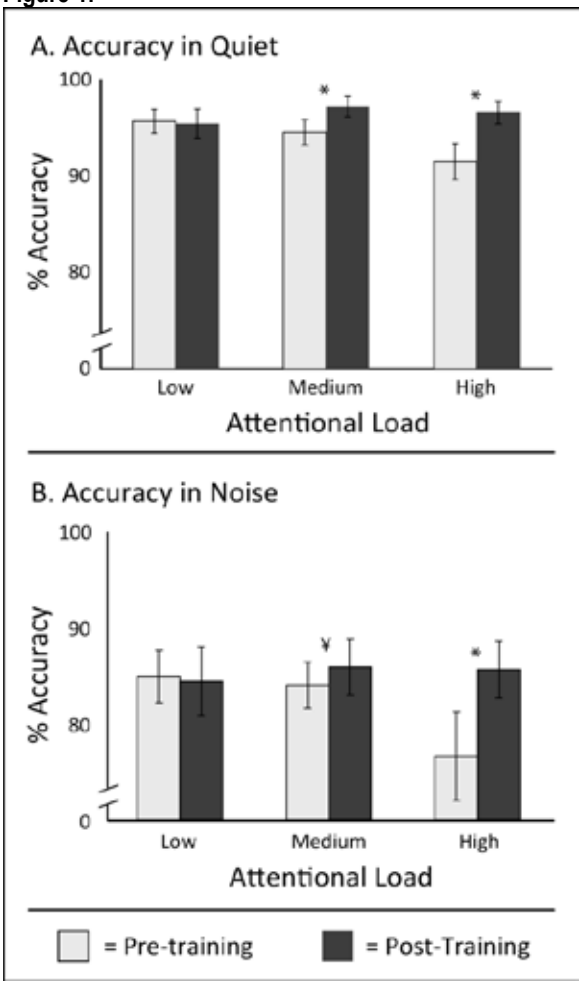


Figure 2.

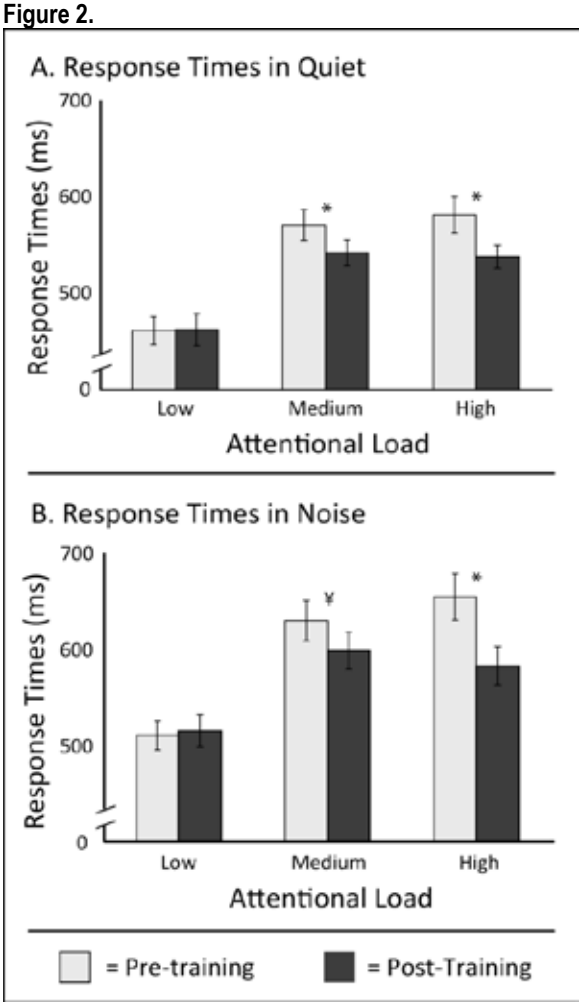
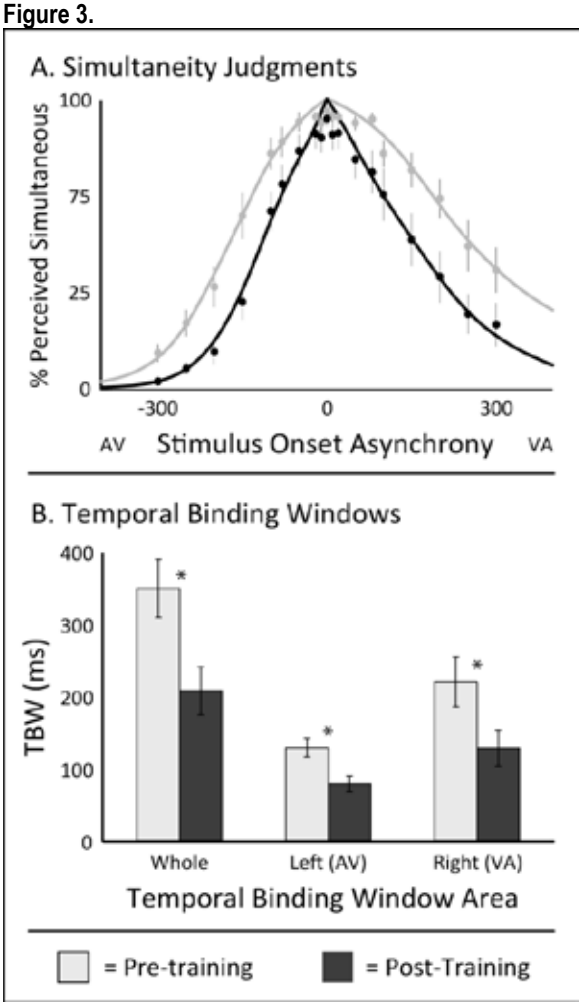


Figure 3.



CW 1759-50 An Ultra-Short Acting Nondepolarizer Immediately Antagonized at Any Time by L-Cysteine

John J. Savarese, M.D.[1]; Hiroshi Sunaga, M.D.[1]; Matthew R. Belmont, M.D.[1]; Matthew Murrell, M.D., Ph.D.[1]; Paul M. Heerdt, M.D., Ph.D.[1]; Jeff McGilvra, Ph.D.[2]
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Background: CW 1759-50 has been developed to reduce histaminoid phenomena in an ultra-short acting nondepolarizer; when compared with gantacurium (GW 280430A) its safety ratio [ED for histaminoid circulatory, pulmonary and cutaneous phenomena/NMB ED95] is approximately four to seven times greater in monkeys and dogs versus that of gantacurium (unpublished data). CW 1759-50 is ultra-short acting because the molecule is inactivated by bodily L-cysteine in a chemical reaction. In this study we tested spontaneous recovery and antagonism of 1759-50 blockade by exogenous L-cysteine at two key points: One minute following a bolus dose of 4x ED95 (0.20 mg/kg) (point A) and one minute following discontinuation of continuous infusions (point B).

Methodology: With IACUC approval male rhesus monkeys weighing 9-18 kg were studied under isoflurane/N2O/O2 anesthesia (1.5-2.0 %); twitch, TOF, blood pressure and heart rate were recorded continuously. Controlled ventilation was maintained and temperature, ETCO2, and SpO2 were kept within normal limits under continuous monitoring. ED95 for NMB was calculated. Neuromuscular function was measured mechanomyographically. Total duration (injection to 95% twitch recovery) following ED95 and 4x ED95 dosage was determined. Continuous infusions of CW 1759-50 were given to monkeys for durations of 30-120 min., where 99-99.5% block was maintained. Rate of spontaneous recovery following infusion was measured as the interval of twitch recovery from 5 to 95 percent twitch height. Intervals [5-95% recovery] following ED95, 4xED95, and infusions were compared.

Reversal of neuromuscular blockade by L-cysteine was measured at two key points: (A) at +1 min after injection of 4x ED95 (0.20 mg/kg); (B) at 100% twitch inhibition 1 min. after cessation of continuous infusion. The [5-95% interval] following L-cysteine reversal was compared with spontaneous recoveries following bolus dosage and infusion.

Results: Rate of spontaneous recovery [5-95% interval] following bolus dosage (1x – 4x ED95) and infusion did not differ. Rate of accelerated recovery (reversal) by L-cysteine also did not differ. (Table).

Discussion: The data indicate that recovery from 1759-50 blockade, whether spontaneous or L-cysteine accelerated (reversal) is unaffected by bolus dosage or infusion. The neuromuscular properties of 1759-50, together with its reduced association with histaminoid phenomena (vis-à-vis gantacurium) suggest that the new compound may present an improved profile in human subjects.

Drug Infusion System Manifold Dead-Volume Impacts the Delivery Response Time to Changes in Infused Medication Doses In Vitro and Also In Vivo in Anesthetized Swine

Robert A. Peterfreund, M.D., Ph.D.[1]; Mark A. Lovich, M.D., Ph.D.[2]; Matthew G. Wakim, B.S.[3]; Abraham Wei, B.S.[2]; Michael J. Parker, M.D.[4]
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Background: Intravenous infusion systems can be configured with manifolds connecting multiple drug infusion lines to catheters. Prior in vitro studies suggest that there may be significant lag times for drug delivery to reflect changes in infusion rates set at the pump, especially with low drug and carrier flows and larger infusion system dead-volumes. Manifold design can contribute significantly to infusion system dead-volume and thus augment delays. We hypothesized that the time course of physiological responses to drug infusion in vivo reflects the impact of dead-volume on drug delivery.

Methods: The response to changes in set epinephrine infusion rate was compared for high and low-dead-volume manifolds in vitro and in vivo. A manifold consisting of four sequential stopcocks with drug entering at the most upstream port was contrasted with a novel design comprised of a tube with separate coaxial channels meeting at the downstream connector to the catheter, which virtually eliminates the manifold dead-volume. The kinetics of both epinephrine (3 ml/hr, 0.1 mcg/kg/min) exiting the catheter in vitro and the contractile response (left ventricular max dP/dt) in vivo were characterized during initiation and cessation of drug infusion with constant carrier flow (10 ml/hr). The time to first change in drug delivery or biologic response (T0), and the time to 50% and 90% of steady-state values (T50 and T90) were calculated for initiation and cessation of drug infusion.

Results: The time to steady-state after initiation and cessation of drug infusion, both in vitro and in vivo was much less with the coaxial low-dead-volume manifold than with the high-volume manifold design. The low-dead-volume manifold in vitro led to approximately 5-fold lower T50 and T90 than for the high-dead-volume manifold. In vivo, the T0, T50, and T90 were 1.6 -3.8-fold larger for the high-dead-volume manifold. The T50 was approximately 3 minutes longer in vivo than in vitro, a difference which likely represents the kinetics of drug circulation and effect.

Conclusions: The architecture and dead-volume of the manifold portion of an infusion system impact the in vivo response to changes in drug infusion rate set at the infusion pump. Thus, the time course for epinephrine's circulation in blood and biologic action, which should be similar regardless of manifold design, does not overwhelm the drug delivery delays arising from the infusion system dead-volume.

Hypobaric Oxygenation During Cardiopulmonary Bypass Eliminates Gaseous Microemboli and Reduces Microvascular Injury in Swine

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Introduction: Successful cardiac surgeries are frequently complicated by cognitive deficits of multifactorial etiology that degrade quality of life and increase healthcare costs. Gaseous microemboli (GME) contribute to several possible etiologies, and they occur by the thousands during cardiopulmonary bypass (CPB). Vasooclusive GME cause tissue ischemia and damage endothelium, leading to vascular dilation and permeability, activation of platelets and clotting cascades, and recruitment of complement and cellular mediators of inflammation. We previously presented a novel approach to oxygenation that practically eliminates GME delivery from the CPB circuit. Here, we extend our mechanistic understanding of GME removal and assess the impact of hypobaric oxygenation on brain tissue in swine.

Methods: Hypobaric oxygenation was performed using a sealed hollow fiber microporous membrane oxygenator and 100% O2 sweep gas at variable subatmospheric pressures. The control condition used O2/air sweep gas at ambient pressure. Dissolved N2 was measured by mass spectrometry. GME were counted and sized using multisite Doppler detection in the CPB circuit: before and after the oxygenator, after the filter, and just before the patient. A veterinary pathologist examined formalin-fixed brain tissue in hematoxylin/eosin sections. A blinded observer measured dilated capillaries (SCAD) in 10x fields of white matter adjacent to the lateral ventricle. Data presented use mean ± SEM and Student's T-test.

Results: We hypothesized that subatmospheric sweep gas pressures would lower O2 partial pressures and achieve normoxic blood gas values while denitrogenating the blood and tissues of the patient, thereby accelerating reabsorption of air from GME into the aqueous phase. Indeed, hypobaric oxygenation denitrogenated blood by at least 85 +/- 1% from baseline (n=3, $P<0.001$). GME removal by the oxygenator, by the arterial filter, and in flowing blood were all substantially improved under hypobaric conditions (see Figure). Analysis of brain tissue revealed normal cytoarchitecture in grey matter of the frontal lobe, thalamus, mesencephalon, cerebellum, and medulla. SCAD, known indicators of microvascular injury after embolization, were 56 +/- 15% more numerous and occupied 95 +/- 29% more area in periventricular white matter from control animals compared with those maintained with hypobaric oxygenation ($p<0.001$).

Conclusions: We previously presented that hypobaric oxygenation safely achieves stable gas exchange during CPB in swine while practically eliminating GME delivered to the animal. Here, we describe the mechanism of GME removal by confirming that the sum of partial pressures of dissolved gases in blood is reduced through denitrogenation. Our data confirm that GME removal is enhanced not only in the oxygenator, but also in the arterial filter and in flowing blood of the CPB circuit, consistent with reabsorption of bubbles into the aqueous phase. Histologic data suggest that hypobaric oxygenation preserves grey matter cytoarchitecture in the brain, and may limit end organ microvascular damage. Hypobaric oxygenation is a promising adjunct to arterial filtration for elimination of GME that we hope may improve neurologic outcomes following cardiac surgery.

Complications of Continuous Intrathecal Catheters in Obstetric Patients

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Our institution takes care of a significant number of high-risk obstetric patients. Therefore, it is a common practice to place intrathecal (IT) catheters in these patients (morbidly obesity, significant pulmonary/ cardiac disease, difficult epidural catheter placement), or following accidental dural puncture (ADP).

After IRB approval, the medical records of all obstetric patients undergoing IT catheter placements from 2001 to 2012 were retrospectively identified from the Anesthesiology Quality Database and Medical records. The intrathecal catheters were placed for vaginal or cesarean delivery using 17G Tuohy needle and 20 G epidural catheters.

Results: A total of 761 patients had Intrathecal (IT) catheter placements during the study period. This included 110 intentional IT catheter placements and 651 accidental dural punctures (ADP group). Out of the 651 catheters, 634 catheters were placed intrathecally after noticing the dural punctures. The rest of the catheters (17) were presumed to be placed epidurally and later discovered to be intrathecal.

Over half (51%) of the 111 intentional catheters were placed due to morbid obesity (BMI 38-81 kg/m2). About 25% were placed following difficult epidural catheter placements or failed epidural catheters. The reason was not documented in 8% of patients (9). The rest of the catheters (17%) were placed in patients with significant cardiac, pulmonary disease, or anatomical abnormalities involving the spine.

Catheter Failures: A total of 45 IT catheters failed in this study. Therefore, the overall failure rate of IT catheters was 5.9% (45/761). The failure rate was 7.1 % in the intentional group (8) and 5.7% in the ADP group (37).

Respiratory Problems: Four patients in the ADP group had high block requiring intubation and ventilation.

Post dural puncture headache (PDPH): There were 312 patients (40.9%) who developed PDPH. Out of these 99 patients (31%) required epidural blood patch treatment. Therefore the epidural blood patch incidence was 13% (99/761).

Neurological problems: There were no cases of meningitis, arachnoiditis, cauda equina syndrome or epidural hematoma identified in this series. However, three patients from the ADP group did present with postpartum headache initially attributed to PDPH, but they were later diagnosed with neurological conditions unrelated to IT catheter placement.

Discussion: Intrathecal catheters are infrequently used in the obstetric patients due to fear of complications such as post dural puncture headache (PDPH), or more severe complications such as infection and neurological damage. However, no infections or neurological damage occurred in this series. Since IT catheter use can be an attractive option for parturients with certain comorbities, the relative risk of PDPH, which is a treatable condition, should be weighed against the many advantages of this neuraxial technique.

Development of Stable Volatile Anesthetic Nano-Emulsions for Intravenous Injection at Sub-Anesthetic Concentrations: Preliminary Investigations

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Objectives: Since the 1960s there have been several reports describing the development of phospholipid or PFC-based emulsions of volatile anesthetics (VA) intended for intravenous injection (VA) as general anesthetics (GA). (1) However, to date no formulation of this type has progressed to clinical trials, primarily due to the fact that VA emulsions, in order to induce GA in either large animals or humans at clinically relevant doses, require VA concentrations exceeding 20% v/v, which are inherently highly unstable. In contrast, the impetus for the development of VA emulsions in our laboratory is to attempt to harness the therapeutic potential of the pre- and post-conditioning properties of VA, which may require much lower (sub-anesthetic) VA concentrations to be clinical effective.

Methods: We manufactured nano-emulsions of 4.5% v/v Isoflurane (ISO) in 30% Intralipid and tested stability over time in sealed or open containers at 40C and 25C, by measuring ISO concentration by HPLC (evaporation) and change in particle size (coalescence) by dynamic light scattering (DLS). We also tested GA potency (ED50/LD50) and toxicity in male Lewis rats (300-350g).

Results: Our 4.5% ISO/30% Intralipid nano-emulsion retained about 93% of its original concentration when stored in open containers @ 25ºC for 2 days (Fig 1-A) and 99% after 58 days in sealed containers at 4°C (Fig 2-A). There was no significant change in nano-particle size after 58 days at 25°C in sealed containers (451.7 ± 24.6nm vs. 371.3 ± 27.8nm; Fig 1-B) or after 58 days in sealed containers at 4°C (451.7 ± 24.6nm vs. 469.5 ± 49.1nm; Fig 2-B). ED 50 of ISO emulsion was 0.073±0.003 mLISO/Kg and LD50 was 0.205±0.003 mLISO/Kg. (Fig 3). ISO infusion resulted in induction time of 126.0 ± 14.2 seconds (Fig 4) and recovery time of corneal reflex, forepaw reflex, and awake: 45.3 ± 10.1, 83.3 ± 18.5, and 124.5 ± 14.3 seconds, respectively. Laboratory toxicity testing was negative (Fig 5).

Conclusions: Our 4.5% ISO/30% intralipid nano-emulsion is ultra-stable with extended shelf life when stored in open or sealed containers at either 40C or 250C, with anesthetic potency and relative safety in rats. Further standard pharmacological testing is in progress.

References

1. KRANTZ JC Jr., et. al.: A note on the intravenous use of anesthetic emulsions in animals and man with special reference to methoxyflurane, Anesthesiology. 1961 May-Jun;22:491-2

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Figure 1

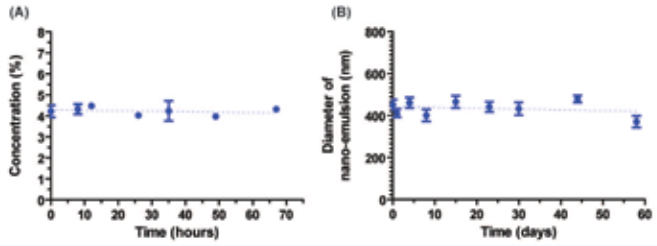
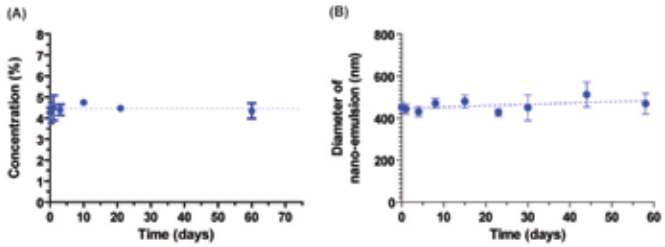


Figure 2



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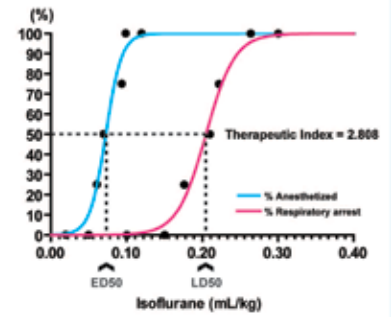

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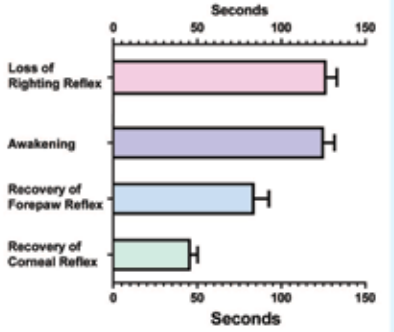
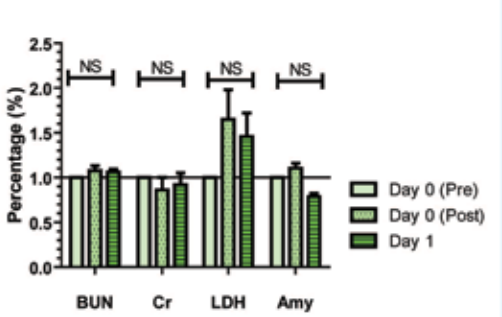


Figure 5



Controlling Anesthetic Vapor Concentration Using Temperature Regulation

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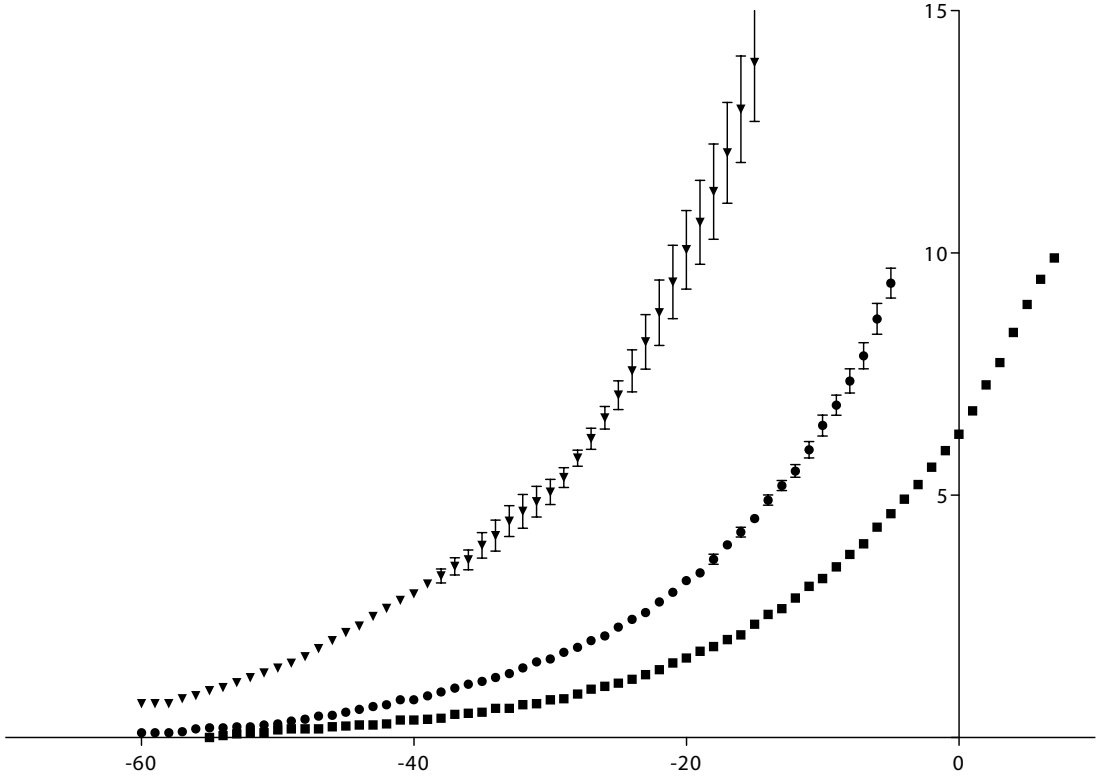
Introduction: The saturated vapor pressure of volatile agents is temperature dependent. We hypothesized that clinically relevant concentrations of anesthetic vapor could be achieved at very low temperatures (less than 0°C). We sought to determine the temperature of an anesthetic vapor, measured at 1 atmosphere of pressure, at which the minimum alveolar concentration (MAC) of the agent is delivered. We referred to this temperature as the "T-MAC" of the agent.

Methods: Volatile anesthetics were placed in an aluminum vessel, which was partially submerged in a low temperature bath consisting of dry ice, ice, and salt water. A fresh-air inflow line (with a flowmeter) provided a constant flow of 1 L/min, and waste vapor was exhausted into a fume hood. A standard sample line was connected to an anesthesia gas monitor (POET II, Criticare Systems, Inc., Waukesha, WI). Agent temperature was measured using a thermometer, and concentrations were recorded at intervals of 1-degree Celsius. Separate experiments were performed using isoflurane, sevoflurane, and desflurane. Each experiment was repeated 5 times.

Results: Each of the agents was successfully cooled to a temperature <50°C. Plots of anesthetic concentration versus temperature were created using GraphPad statistical software (GraphPad Software, La Jolla, CA). (Figure 1) Each point on the curve represents an average of 5 experiments, and the error bars represent the standard error of the mean. Final temperatures for T-MAC were as follows: Isoflurane, -35°C (Anesthetic concentration 1.1± 0.04%, n=5); Sevoflurane, -16°C (2.2±0.02%, n=5); and Desflurane, -26°C (6±0.2%, n=5). To exploit these relationships, we constructed a temperature-controlled anesthetic vaporizer. Using this device we were able to achieve sustained delivery of 1 MAC (2.2±0.02%, n=3) of sevoflurane for 1 hour at T-MAC (-16°C) sevoflurane.

Conclusion: We described the temperature/saturated vapor concentration relationship at clinical concentrations for isoflurane, sevoflurane, and desflurane, and established the T-MAC for each of these agents. It is possible to exploit this relationship in order to deliver clinical concentrations of volatile anesthetic using technology that is distinct from currently available devices. We have constructed a novel anesthetic vaporizer that uses these relationships and can deliver clinically relevant concentrations of sevoflurane.

Figure 1. Cooling anesthetic agents to very low temperatures leads to clinically relevant concentrations of anesthetic.



ADM-O 52 (67)

A Psychoacoustic Analysis of Alarm Sounds and Perceived Urgency

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Introduction: Guidelines for audible alarm design (1) include matching perceived urgency to alarm source severity. However, we recently found urgency mismatch among IEC alarms in attending and resident anesthesiologists (2). It has been suggested that increased heterogeneity might improve alarm function (3). We designed an arbitrary set of more complex experimental alarm sounds. Then we investigated the relation between perceived urgency and auditory features in the IEC and experimental sets using methods from music engineering. We hypothesized that increasing the auditory dimensions in the experimental set could provide more psychoacoustic substrates (i.e., auditory features) with which to encode urgency, and that relative to the IEC alarm set, the experimental set would display more auditory features that correlate with perceived urgency.

Methods: Twenty-one music student subjects were presented with 16 IEC and 8 experimental alarms in random order and asked to rate the alarms on a nine-point Likert scale for perceived urgency. Next, over 300 auditory features that describe dynamics, rhythm, spectral, timbral and tonal characteristics were computed from the IEC and experimental sounds using MIRToolbox in MATLAB and compared to how each alarm sound was rated for urgency by subjects. Significance was considered to be $p<0.05$ and a feature-perceived urgency correlation coefficient, $r>0.25$ or $r<-0.25$.

Results: In the IEC alarm set, the only significant auditory feature that correlated with perceived urgency was the magnitude of the spectral centroid periodicity ($r=0.9$). Analysis of the experimental alarm set yielded five significant auditory feature correlations: standard deviation and mean of the rhythmic attack slope, entropy of tonal mode and harmonic change, and the mean spectral roughness (Fig 1).

Discussion: The results suggest that low auditory dimensionality and complexity of the IEC alarm set limit its ability to induce urgency since only one auditory feature was found to significantly correlate with perceived urgency. In comparison, our experimental alarm set (designed with expanded auditory dimensions, but without significant forethought) yielded a more robust and descriptive correlation between auditory features and perceived urgency. Though this study is limited by being conducted in a laboratory with non-clinicians and by ignoring background and non-alarm sound impacts on urgency perception, the results suggest dimensional heterogeneity can increase the number of manipulatable auditory features available for urgency encoding and guide future alarm development. We are currently applying our methodology to characterize the entire operating room soundscape, and the relation between its auditory features and subjective perceptions by anesthesiologists in a simulated operating room.

References:

1. IEC 60601-1-8 2003
2. Bennett+. ASA 2011 Abstract
3. Edworthy+. Int J Ind Ergonomics 2011;41:136-46

ADM-O 53 (20)

Percutaneous Fiber Optic Monitoring for Spinal Cord Ischemia

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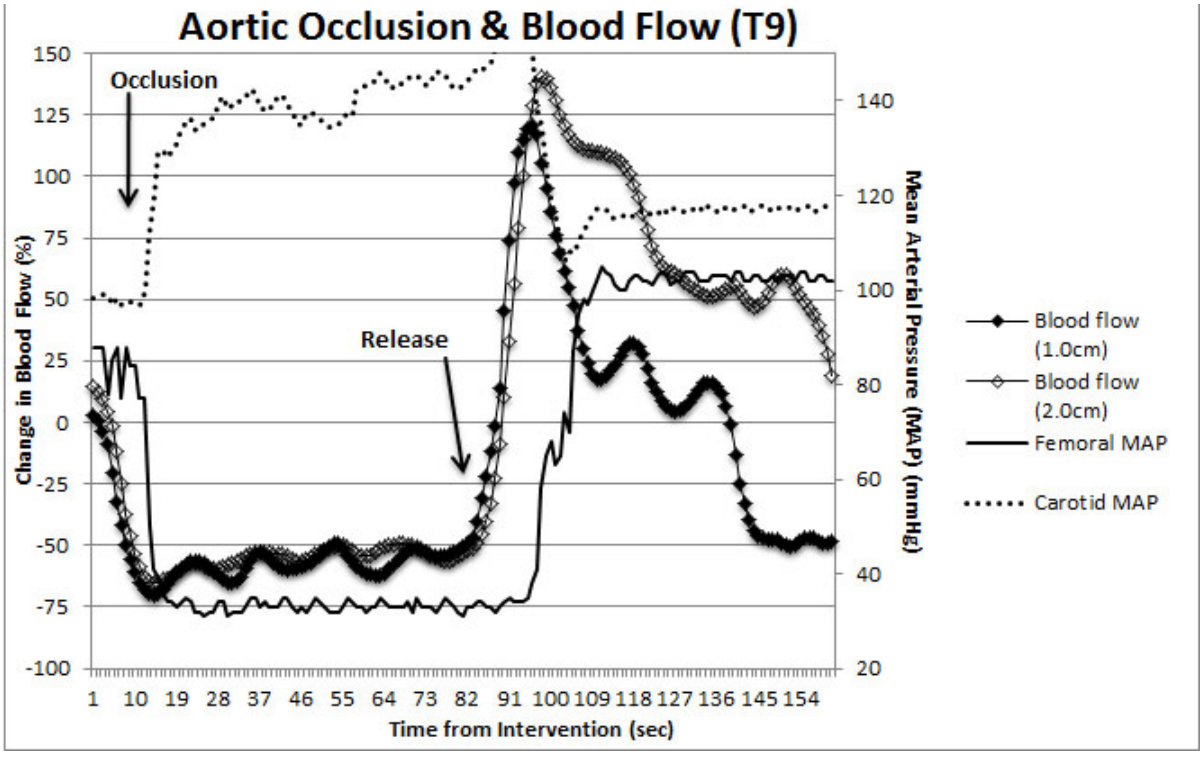
Introduction: Spinal cord ischemia may result in paralysis and paraparesis after trauma, major vascular, spine and spinal cord surgery. Current methods employed to detect spinal cord ischemia, based upon electrophysiology, are indirect, temporally insensitive, nonspecific, and cumbersome.

Methods: We have developed a prototypical fiber optic device based on Diffuse Correlation Spectroscopy (DCS) and Diffuse Optical Spectroscopy (DOS) principles that allow for the detection of changes in spinal cord blood flow and oxygenation. The device has been tested in Dorsett sheep. We employed a linearly arrayed clinical prototype, with a single source and two detectors. Under general anesthesia, femoral and carotid arterial lines were placed. An intra-aortic balloon was advanced to the common cephalic root. A left atrial catheter was placed for the injection of microspheres for quantification of spinal cord blood flow by a proven standard. The fiber optic probe was introduced into the epidural space via Touhy needle and advanced cephalad under fluoroscopic guidance. Spinal cord blood flow and oxygenation responses to pharmacologic interventions (phenylephrine-400ug boluses and nitroprusside-400ug boluses) and aortic occlusion were measured at multiple levels. Spinal cord blood flow and oxygenation were recorded continuously via the fiber optic probe.

Results: The fiber optic probe immediately detected increased blood flow and oxygenation in response to hypertension, and decreased flow and oxygenation in response to hypotension. Aortic occlusion resulted in an immediate fall in spinal cord blood flow and oxygenation. Previous work in our lab has demonstrated blood flow responses from subdural, epidural, or percutaneously placed probes to be indistinguishable. Blood flow measurements from the DCS probe were directionally in agreement yet more robust than measurements obtained from microsphere measurements. Data from this and previous experiments demonstrates that the fiber optic probe is sensitive, successfully detecting changes in spinal cord blood flow associated with acute hypertension in 12/12 trials (100%), acute hypotension in 9/9 trials (100%), aortic clamping in 14/14 trials (100%), and selective ligation of vertebral arteries in 1/1 trial. In a series of experiments, the mean change in flow associated with the hypertensive and hypotensive challenges was (+) 51 ± 11% and (-) 39 ± 11% respectively. The instantaneous flow:pressure response correlation was R2 = 0.92, p < .001. Rapid pressure autoregulation was seen with pressure changes >≈ 50 torr.

Conclusions: Percutaneous fiber optic monitoring of spinal cord blood flow and oxygenation is feasible and the results of initial testing are promising. This monitoring tool potentially represents an important step forward, offering a new level of accuracy and immediacy in detecting spinal cord ischemia intraoperatively, and in the neurocritical care setting.



Early Potential Biomarker Changes in the Nitric Oxide Pathway in the Exhaled Breath Condensate of Ventilated Respiratory Disease-Free Surgical Patients

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Background: Measuring exhaled breath condensate (EBC) biomarkers is increasingly common for understanding multiple respiratory diseases, including the Acute Respiratory Distress Syndrome (ARDS). No information exists on the early changes in potential EBC biomarkers that might be occurring during the initiation of ventilation in healthy patients. We hypothesized that EBC analysis would detect early ventilator-induced biomarker changes in the nitric oxide pathway in healthy patients undergoing an elective knee replacement.

Methods: After obtaining IRB approval and patient consent, we collected EBC and plasma samples from 30 non-smoking patients with BMI<35 and no respiratory disease, scheduled for an elective knee replacement under general anesthesia. Anesthesia was induced and maintained in all patients with propofol, fentanyl and rocuronium. Patients were randomized to receive ventilation with a tidal volume of 6 ("VT6") or 10 ("VT10") mL/kg of predicted body weight (PBW). Respiratory rate was titrated for eucapnia at PEEP of 5cmH2O and 0.5 inspiratory oxygen fraction. EBC samples were collected using a customized adaptation of the commercially available RTubeTM (Respiratory Research) into the expiratory limb of the respiratory circuit for 20 minutes, immediately after initiation of mechanical ventilation ("baseline") and 60min later ("60min"). Physiology parameters (hemodynamics, respiratory) and clinical outcomes were recorded. Nitric oxide (NO) metabolites (nitrite, nitrate, arginine, ADMA, SDMA) were analyzed by HPLC in the EBC and plasma, compared with literature-reported values and correlated with patients' characteristics.

Results: EBC NO metabolite levels were measurable and comparable to literature-reported values in healthy controls. EBC NO metabolite levels did not correlate with patient's age, weight or body mass index. Without achieving statistical significance, the average EBC NO levels increased in the VT10 group from baseline to 60min but, in contrast, were unchanged in the VT6 group. 3 patients in the VT10 group, but none in the VT6 group, had a ≥100% increase in EBC NO at 60min compared to baseline. No differences were found in plasma NO metabolites from baseline to 60min, or in relevant physiology parameters or clinical outcomes between the VT6 and VT10 groups. In all samples pooled together, EBC NO correlated with EBC arginine (Pearson coef. 0.562, p=0.015), plasma NO (Pearson coef. 0.348, p=0.007) and plasma ADMA (Pearson coef. -0.334, p=0.12).

Conclusion: Exhaled Breath Condensate research is feasible in ventilated surgical patients and may help increase our understanding of the early changes in lung oxidative stress. Additional understanding of the individual variability and time course of EBC biomarkers could improve the validation and interpretation of a noninvasive research tool with potential diagnostic and therapeutic opportunities.

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Hemodynamic Collapse Following Pericardiectomy During Emergency Pulmonary Embolectomy

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Acute pulmonary embolism (PE) is a major cause of morbidity and mortality in patients across all demographics. Studies have demonstrated perioperative mortality ranging from 9% to as high as 77% (Leacche, Carvalho) with emergency surgical pulmonary embolectomy. Anesthetic management of acute pulmonary embolectomy has been limited to case reports and small case series with the largest to date describing a 19% incidence of need for emergent cardiopulmonary bypass (CPB) following induction of anesthesia (Rosenberger). In our retrospective review of 35 patients from 2008-2012 we have identified a novel second period of hemodynamic instability that coincides with pericardiectomy.

Introduction: Acute pulmonary embolism is a major cause of morbidity and mortality in the cardiac surgical population. Significant hypotension necessitating emergent CPB following induction of anesthesia has been well described. However, we have identified a second period of hemodynamic instability necessitating emergency cardiopulmonary bypass immediately following pericardiectomy. We reviewed our institutional data for patients undergoing acute pulmonary embolectomy from 2008-2012 and present our initial findings.

Methods: After IRB approval we performed a retrospective review of patient's undergoing emergent pulmonary embolectomy from January 2008 to December 2012 using the cardiac surgery department's database of surgical patients. Patient charts were reviewed for anesthetic records, perfusion records, and surgeon operative notes. Need for urgent bypass was identified if hemodynamic instability with a need for rapid institution of CPB was identified in any of the records. Patient information was further reviewed for potential risk factors for hemodynamic instability.

Results: 46 patients were found to have undergone surgery for acute pulmonary embolism. 6 patients were excluded as they were either intubated prior to the operating room or had received CPR prior to induction of anesthesia. An additional 5 patients developed cardiovascular collapse requiring emergent CPB following induction of general anesthesia and were excluded. Of the 35 patients included in the study, 17% developed severe systemic arterial hypotension following pericardiectomy. These hemodynamic changes were refractory to vasopressor and inotropic support and patients ultimately required emergent initiation of CPB. Table 1 details patient characteristics who required emergent CPB. Patients were considered to be in cardiogenic shock if their cardiac index was less than 2.2mL/min/ m2 and their systolic blood pressure was < 90 mmHg or they required inotropic or vasopressor support prior to the operating room. No risk factors were identified in the patients that required emergent CPB with pericardiotomy (table 2).

Discussion: This is the first report of a secondary critical period during acute pulmonary embolectomy that may require emergent institution of CPB. Our review demonstrated a 17% incidence of cardiovascular collapse. Risk factors were the same regardless of demographics, right ventricular function, and initial acid-base status, suggesting that all patients are at risk. While the mechanism is unclear, we postulate that sudden increased venous return after pe

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Table 1: Post-Pericardiotomy Instability Characteristics (N=6)

	Age	BMI	RV Failure	Hct	HTN	Smoker	COPD	LVEF	Shock	Preop pH	Intraop pH	Lactic Acid	HR Change
	82	28	unknown	43	yes	no	no	>55%	N	7.35	7.32	1.1	105-->80
	18	21	mild	41	no	no	no	50%	N	7.3	7.36	1.9	120-->110
	50	37	mild	46	no	no	no	>55%	N	NA	7.22	1.0	110-->100
	25	40	severe	42	no	no	no	>55%	Y	NA	7.48	0.6	100-->100
	72	30	severe	27	yes	yes	no	55%	N	7.24	7.33	2.0	110-->90
	46	42	moderate	38	yes	no	no	>55%	N	7.43	7.25	0.8	95-->85
mean	49	33		39.5							7.33	1.2	

Table 2: Potential Risk Factors for Post-Pericardiotomy Instability						
	Unstable (n=6)		**Stable (n=29)**		**P value**	
HTN	3	50%	15	52%	> 0.999	
Smoker	0	0%	4	14%	> 0.999	
Prior AMI	1	17%	5	17%	> 0.999	
COPD	0	0%	1	3%	> 0.999	
Shock	1	17%	4	14%	> 0.999	
BMI	33		33		> 0.999	
RV failure						
mild	2		4		0.27	
moderate	1		13		0.4	
severe	2		7		> 0.999	
unknown	1		5			
Inotrope / Pressor	3	50%	10	34%	0.64	

Patient Selection for Outpatient Surgery: Identifying Those at High Risk for Major Complications

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Introduction: Driven by improvements in perioperative care as well as economic pressures, the proportion of ambulatory surgeries performed annually in the US has increased dramatically over the past three decades, currently comprising over 60% of all surgical procedures.(1) However, despite advances in perioperative care affording very low rates of complication in surgeries performed on an outpatient basis, a severe lack of knowledge exists regarding risk factors for outpatient surgical morbidity and mortality.(2) There are no multicenter clinical data guiding which patients should be selected for – or excluded from – ambulatory surgery center locations during common outpatient procedures. To this end, we used a national database of prospectively collected data to evaluate for perioperative patient and surgical characteristics associated with increased risk of perioperative morbidity or mortality following common outpatient surgical procedures.

Methods: We performed a prospective review of all adults undergoing common outpatient surgical procedures using the Participant Use Data File of the American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) from 2005-2010. Common outpatient surgical procedures were identified through a combined review of the most common surgical Current Procedural Terminology codes provided by Blue Cross Blue Shield of Michigan and Medicare publications. The study population was restricted to adult outpatients and those admitted on the day of surgery. The primary outcome was perioperative morbidity or mortality, defined as any number of perioperative surgical, anesthetic, and medical adverse events that may be difficult to address in the ambulatory surgery center or outpatient setting. Non-parsimonious logistic regression modeling was performed to determine independent predictors of our outcome while controlling for surgical complexity.

Results: Of the 244,397 cases included in our study, 629 (0.3%) experienced a perioperative morbidity or mortality; all 107 mortalities were postoperative. The most common perioperative morbidities included failure to intubate, intraoperative blood transfusion, surgical site infection, postoperative pneumonia, and unplanned postoperative re-intubation. Controlled for surgical complexity, seven independent risk factors were identified: history of cancer, paraplegia/quadriplegia, steroid use, chronic obstructive pulmonary disease, history of transient ischemic attack/stroke, age >80 years, and age 71-80 years (Figure).

Discussion: Our study confirms the safety of performing common outpatient surgical procedures, as demonstrated by an exceedingly low rate of perioperative morbidity and mortality. Our data are the first prospectively collected clinical data to identify specific factors that increase the risk of morbidity and mortality with outpatient surgery. Through a careful evaluation of such risk factors, a more objective patient screening for outpatient and ambulatory surgery center operations may improve clinical decision-making.

References:

1 Cullen KA, et al. Ambulatory surgery in the United States, 2006. Natl Health Stat Report 2009: 1-25.
2 Bettelli G: High risk patients in day surgery. Minerva Anestesiol 2009; 75: 259-68. Epub 2008 Oct 23.

Relationship Between Endogenous Opioid Function and Opioid-Related Side Effects

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Factors contributing to differential responses to opioid analgesic medications across individuals are not well understood. This study tested whether individual differences in endogenous opioid systems contribute to variability in side effects experienced following administration of a prototypic exogenous opioid analgesic. Participants included 18 healthy individuals and 26 individuals with chronic low back pain (CLBP), all using no opioid analgesics. Participants attended 3 identical sessions during which they received either intravenous naloxone (8mg), morphine sulfate (0.08mg/kg), or saline placebo, and then underwent an ischemic forearm laboratory pain task followed by a computerized heat pain task (Medoc TSA-II). All subjects described their opioid-related side effects with Zacny's 26-item VAS opioid effects questionnaire1. Endogenous opioid function scores were computed by subtracting mean pain intensity variables recorded during the placebo condition from mean pain intensity variables during the naloxone condition (higher positive scores reflect greater endogenous opioid function). Morphine condition side effects were analyzed for associations with these derived endogenous opioid function scores. No significant differences in side effects were noted between healthy individuals and individuals with CLBP, so these groups were combined for analyses. Correlation analyses of opioid side effects revealed significant (p's<0.05) negative correlations between endogenous opioid activity and reports of feeling "stimulated," "tingling," "elated," and "good." There were significant (p's<0.05) positive correlations observed with reports of feeling "irritated" and "bad." Overall, results suggest that elevated endogenous opioid activity is associated with fewer positive and more negative psychoactive effects following administration of opioid analgesics.

References

1. Psychopharmacology (Berl). 2003; 170: 242-254.

High-Sensitivity Cardiac Troponin T in Prediction and Diagnosis of Myocardial Infarction and Long-Term Mortality After Non-Cardiac Surgery

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Background: Perioperative myocardial infarction is a serious complication after non-cardiac surgery. We hypothesized that preoperative baseline cardiac troponin T detected with the novel high-sensitivity (hs-cTnT) assay will identify patients at risk of acute myocardial infarction (AMI) and long-term death after major non-cardiac surgery.

Methods: This was a prospective cohort study within the Vitamins in Nitrous Oxide (VINO) trial (n=608). Patients had been diagnosed with or had multiple risk factors for coronary artery disease and underwent major non-cardiac surgery. Cardiac troponin I (contemporary assay) and troponin T (high-sensitivity assay), and 12-lead electrocardiograms were obtained before and immediately after surgery and on postoperative day 1, 2 and 3.

Results: At baseline before surgery, 599 patients (98.5%) had a detectable hs-cTnT concentration and 247 (41%) were above 14 ng/L (99th percentile). After surgery, 497 patients (82%) had a rise in hs-cTnT (median ∆hs-cTnT +2.7 ng/L [IQR 0.7, 6.8]). During the first three postoperative days, 9 patients (2.5%) with a preoperative hs-cTnT <14 ng/L suffered from AMI, compared to 21 patients (8.6%) with a preoperative hs-cTnT >14 ng/L (odds ratio, 3.67; 95% CI 1.65 – 8.15). During long-term follow-up, 80 deaths occurred. The 3-year mortality rate was 11% in patients with a preoperative hs-cTnT concentration <14 ng/L compared to 25% in patients with a preoperative hs-cTnT >14 ng/L (adjusted hazard ratio, 2.17; 95% CI 1.19 – 3.96).

Conclusions: In this cohort of high-risk patients, preoperative hs-cTnT concentrations were significantly associated with postoperative myocardial infarction and long-term mortality after non-cardiac surgery.

ADM-O 59 (77)

The Use of Preoperative Resources in Low Risk Patients Older Than 65 Years

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Background: Preoperative medical consultations and testing are commonly performed in patients with high medical risk, and multiple studies have addressed the cost and consequences of preoperative testing. Less data are available on the cost and consequences of performing preoperative consultations. We conducted a study to estimate the cost of preoperative consultations and the cost of preoperative testing in a large Medicare population with low pre-operative risk.

Methods: We used a 20% random sample of Medicare part B claims data from 2006, and included all patients who underwent one of four high-volume surgical procedures. We identified level 2 to 5 preoperative consultations (CPT 99242-5 and 99252-5) provided by family practitioners, internists, pulmonologists, cardiologists, or endocrinologists that occurred within 42 days prior to index surgery. We also included office visits (CPT 99202-5 and 99212-5) that exceeded the usual baseline rate of such visits. The primary analysis was restricted to low risk patients as defined by Revised Cardiac Risk Index (RCRI) scores of 0 and 1. We identified all claims for CXR and ECG, and estimated the frequency of common laboratory studies within 42 days of surgery. We used reimbursement rates for 2006 as published by CMS.

Results: The study sample consisted of 227,741 patients, and of those 179,118 (78.6%) had a RCRI ≤1. Overall, 38% of patients had a preoperative consultation, 12% had a preoperative CXR, 32% had an ECG, and 28% had a preoperative blood test. These proportions varied among the selected four surgical procedures. The table reports frequencies of testing and their respective Medicare dollar reimbursement.

Conclusion: These data suggest that there is substantial use of preoperative consultations and preoperative testing among low risk patients undergoing common surgical procedures. Further research is needed to determine whether these data highlight an opportunity to reduce health care costs by implementing more rational use of these resources.

ADM-O 60 (79)

Do Anesthesiologists Matter? Assessing the Variation in Surgical Outcomes Due to Anesthesiologists

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Background: Current Accountable Care Organization guidelines do not attribute any shared savings or costs to the specialty of Anesthesiology. Essentially, current policy considers the anesthetic episode a static "black box" without variable effect on patient outcome, despite mounting mechanistic evidence that the anesthetic has long term impact. These policies are due to the absence of any population level data demonstrating the impact of anesthesiology on surgical outcome variation. We hypothesized that a measurable proportion of outcome variation can be attributed to variation in anesthesiology practice and provider.

Methods: Data was acquired from the Medicare Provider Analysis and Review files, which contain all hospital discharges for Medicare recipient acute care. Using ICD9 procedure codes, we identified all patients who underwent isolated coronary artery bypass graft (CABG) procedures from 2004 to 2007 and linked to Part B fully loaded professional claims to identify the primary surgeon and anesthesiologist using codes. The primary outcome was 30 day all-cause mortality. Using ICD9 diagnoses, patient comorbidity burden was dichotomized into an Elixhauser score. Hospital level data included the total number of beds and the teaching status. High hospital volume was dichotomized and defined as ≥ or < 450 cases per year. Surgeons were divided by case load into quartiles of volume. Additional covariates of interest were age, male sex, and emergent/urgent operation.

Using SAS 9.3, two hierarchical models were developed and the intraclass correlation coefficient (ICC) was calculated based on the estimated variance of the random effect placed into each model. The primary model sought to determine the amount of variability in mortality explained by the anesthesiologist. Therefore, the anesthesiologist was entered as the random effect while the fixed effect covariates were age, sex, Elixhauser score, emergent/urgent, bed size, hospital volume, teaching hospital, and surgeon volume quartiles. A sensitivity analysis evaluating the surgeon random effect was performed.

Results: A total of 295,115 patients were included for analysis. The overall 30-day mortality rate was 4.15% (12,262). The ICC for the primary anesthesiologist model was 3.53%, indicating that 3.53% of the total variability in mortality is explained by the anesthesiologist provider variable. The ICC for the surgeon analysis was 5.12%.

Discussion: After adjusting for patient, procedure, hospital, and surgeon covariates, the anesthesiology provider is responsible for approximately 3.5% of mortality variation in CABG surgery. These are the first data to demonstrate a measurable proportion of outcome variation is attributable to the anesthesiologist. They can help shape reimbursement policy that has historically not incorporated anesthesiology variation into shared savings or costs allocation. Future research must identify which specific practice patterns and clinical interventions are associated with improved outcomes.

References:

D'Errigo et al BMC Medical Research Methodology 2007, 7:29
Finks et al N Engl J Med. 2011;364(22):2128-37
Snijders T, Bosker R: Discrete dependent variables London: Sage Publication; 2000.

Poster Presentations

Organ Protection/Cell Signaling

OP-CS 61 (17)

The Role of the preBötzinger Complex in Opioid-Induced Respiratory Depression is Age-Dependent

Astrid G. Stucke, M.D.[1]; Eckehard A.E. Stuth, M.D.[1]; Ivana Prkic, M.D.[1]; Caron Dean, Ph.D.[1]; Francis A. Hopp, MS[1]; Edward J. Zuperku, Ph.D.[2]
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OP-CS 62 (54)

IL-33/ST2 Signaling Worsens Immune-Mediated Hepatitis From Drug Haptens

Dolores Njoku, M.D.; Sarah Goodman; Joonhee Cho, B.S.; Lina Kim, B.S.; Mark Haham, M.D.
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OP-CS 63 (63)

Junior Faculty Award

A Novel Strategy to Treat Human Pre-Term Labor - Targeting the TMEM16/Anoctamin Chloride Channel in Human Pregnant Uterus

George Gallos, M.D.; Herng-Yu Sucie Chang, Ph.D.; Wen Fu, Ph.D.; Elizabeth Townsend, Ph.D.; Hiromi Funayama, D.D.S., Ph.D.; Charles W. Emala, M.D.
Columbia University

OP-CS 64 (82)

Prolonged Hyperglycemia Abolishes Ischemic Preconditioning in Glomerular Endothelial Cells

Katie J. Schenning, M.D., M.P.H.; Nabil J. Alkayed, M.D., Ph.D.; Michael P. Hutchens, M.D., M.A.
Oregon Health & Science University

OP-CS 65 (85)

Hydrogen Sulfide in High Concentrations Vasodilates the Fetoplacental Circulation in the Dual-perfused, Single Isolated Human Placental Cotyledon

Curtis L. Baysinger, M.D.; Raymond F. Johnson, B.Sc.; John W. Downing, M.D.; Jerod S. Denton, Ph.D.
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OP-CS 66 (1)

Methylnaltrexone Inhibits Opioid- and Growth Factor-Induced Human Lung Cancer Proliferation, Migration and Epithelial Mesenchymal Transition (EMT)

Jonathan Moss, M.D., Ph.D.; Frances E. Lennon, Ph.D.; Tamara Mirzapoiazova, M.D., Ph.D.; Bolot Mambetsariev, Ph.D.; Ravi Salgia, M.D., Ph.D.; Patrick A. Singleton, Ph.D.
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OP-CS 67 (56)

Preservation of B Cells in Intra-abdominal Sepsis Decreases Mortality

Alison Perate, M.D.[1]; Amy Reed, M.D., Ph.D.[2]; Hooman Noorchashm, M.D., Ph.D.[3]; Ali Naji, M.D., Ph.D.[4]; Clifford Deutschman, M.D.[4]
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OP-CS 68 (58)

Endogenous Ubiquinol, Oxidative Stress, and Kidney Injury Following Cardiac Surgery

Frederic T. Billings, M.D., M.Sc.[1]; Jorge L. Gamboa, M.D., Ph.D.[1]; Catherine K. Yeung, Pharm.D., Ph.D.[2]; Danny D. Shen, Ph.D.[2]; Jonathan Himmelfarb, M.D.[2]; Alp Ikizler, M.D.[1]
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OP-CS 69 (62)

Interplay Between Toll-Like Receptors and Complement Factor B In Polymicrobial Sepsis

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OP-CS 70 (22)

MicroRNAs and Anesthetic Cardioprotection in Diabetes

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OP-CS 71 (47)

Critical Role of Interleukin-11 in Isoflurane-Mediated Protection Against Ischemic Acute Kidney Injury

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OP-CS 72 (32)

Resident Travel Award

Novel Chloride Channel Blockers Relax Airway Smooth Muscle: Potential New Tools to Treat Bronchospasm

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The Role of the preBötzinger Complex in Opioid-Induced Respiratory Depression is Age-Dependent

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Background: The preBötzinger Complex (preBC) is considered crucial for respiratory rhythm generation, and opioids applied to the preBC depress respiratory rate in neonatal in vitro preparations(1). However, data in adult animals in vivo point to the pons(2). It is unresolved whether these differences depend on the species, the maturity of the animal or on the experimental preparation.

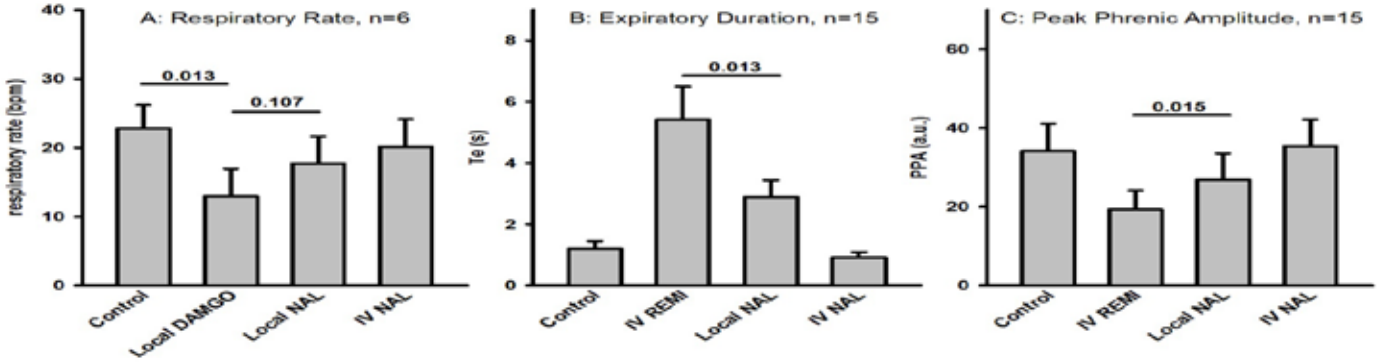
Methods: The study was approved by the local Animal Care Committee and conformed to NIH standards. Three protocols were conducted in young (13-24d, 160-550g) and adult (2.2-5.3 kg) New Zealand White rabbits, which were anesthetized, ventilated, decerebrated and non-vagotomized. 1.: Respiratory neuron activity was recorded and the location of the preBC was determined by the tachypneic response to microinjection of D,L-homocysteic acid, measured from the phrenic neurogram, in vivo. The brainstems were stained for μ-opioid receptors (μORs) post mortem. 2.: The μOR agonist [D-Ala2,N-Me-Phe4,Gly-ol]-enkephalin (DAMGO, 100μM, 70nl (young)/140-400nl (adult)) was injected into the bilateral preBC area and the (depressant) effect on the phrenic respiratory pattern was antagonized with local naloxone (NAL, 1mM, 100nl/200nl). 3.: Phrenic respiratory depression was achieved with intravenous remifentanil (REMI, 0.08-0.5 mcg/kg/min) infusion. NAL (1mM, 70nl/280nl) was injected into the preBC in an attempt to reverse this respiratory depression.

Results: 32 young and 35 adult rabbits were studied. 1.: Ventral respiratory group neurons were recorded between 2 (young)/2.5 mm (adult) caudal of obex and 3/5mm rostral of obex, on average 1.8/2.3mm lateral of midline and a depth of 3.5/5mm from the dorsal surface with the preBC on average at 1.1/1.5mm rostral from obex. This corresponds to an area of μOR stained neurons which includes the nucleus ambiguus(3). 2.: DAMGO injection into the preBC depressed respiratory rate through an increase in expiratory duration (Te) in young animals (fig. 1A) while in adult animals there was a similar depression in 4 animals but no effect in another 6 animals. These effects reversed with local injection of NAL. 3.: Intravenous REMI increased Te (fig. 1B) and decreased peak phrenic activity (PPA, fig. 1C). This effect was partially reversed by NAL microinjection into the preBC in young but not in adult animals.

Conclusion: μORs are present in the ventral respiratory group and preBC in young and adult rabbits. Direct preBC injection of supraclinical concentrations of a μOR agonist affects respiratory rhythm in young and some adult rabbits. However, the depressant effects of an intravenously applied μOR agonist where brain concentrations are about 1000 times lower can only be partially antagonized in the preBC in young animals. Thus the role of the preBC in opioid-induced respiratory depression changes with maturation, which may depend on the changing sensitivity of the brainstem μORs. Sponsored by FAER-MRTG-BS-02-15-2010-Stucke.

(1) Science 1999; 286:1566-8; (2) J Neurophysiol. 2012; 108:2430-41;
(3) Shek et al.: Atlas of the rabbit brain, Karger 1986.

Figure 1: Respiratory Effects of preBC Injection of μOR Agonists and Antagonists in Young Rabbits



IL-33/ST2 Signaling Worsens Immune-Mediated Hepatitis From Drug Haptens

Dolores Njoku, M.D.; Sarah Goodman; Joonhee Cho, B.S.; Lina Kim, B.S.; Mark Haham, M.D.
Johns Hopkins University

Susceptible persons develop immune-mediated drug-induced liver disease (Im-DILI) following exposure to halogenated volatile anesthetics, anti-seizure medications, antibiotics, or non-steroidal anti-inflammatory drugs. Therapeutic options that may alleviate disease have not been fully investigated. IL-33 is a member of the IL-1 family of cytokines that drives Th2 cytokines, cells and injury in asthma (1). In sharp contrast protective roles for IL-33/ST2 were demonstrated in atherosclerosis (2) and experimental CD4+T cell hepatitis induced by Con A (3) In experimental anesthetic Im-DILI, pro-inflammatory cytokines such as IL-1, IL-2, IL-6 as well as IL-13, are detectable during the induction of disease. A prominent feature of this model is neutrophilic hepatitis in addition to mast cells, eosinophils, NK and NKT cells (4). In addition, hepatitis has been successfully transferred to naive mice using CD4+T cells. Demonstration of these cell types in addition to the pro-inflammatory cytokines suggested to us that the ST2/IL-33 pathway has a role in experimental anesthetic Im-DILI. We hypothesized that immune responses signaling through the IL-33/ST2 pathway worsen experimental Im-DILI. To test our hypothesis we utilized our previously identified catalytic site epitope of CYP2E1 (JHDN-5) that had been covalently altered by a trifluroacetyl hapten (TFA) to immunize BALB/c female mice on days 0 and 7 ± IL-33 blocking antibody (Biolegend). Three weeks after the initial immunization liver supernatants were tested for IL-6, TARC, IL-33 and ST2 using ELISA assays (R & D Systems). Hematoxylin and eosin stained slides were scored for inflammation. We found that inflammation ($p<0.01$, Mann-WhitneyU) as well as IL-6, TARC, IL-33 and ST2 ($p<0.05$, Mann-WhitneyU) were significantly elevated in livers from TFA-JHDN-5 – immunized mice when compared to controls. Elevated IL-6 confirmed a key pro-inflammatory cytokine previously associated with this model. Increased TARC supported the presence of Th2 – biased memory/effector CD4+T cells. Elevated IL-33 and its transmembrane receptor ST2 supported our hypothesis and demonstrated Th2-biased immune responses associated with hepatitis. We also found that anti-IL-33 diminished inflammation/injury scores from 2.8 ± 1.1 to 1.6 ± 0.6 (mean ± SD, $p<0.05$, Mann-WhitneyU). Diminished hepatitis following IL-33 blocking antibody confirmed a role for IL-33 in the pathogenesis of Im-DILI. Our preliminary studies suggest that IL-33 may be a therapeutic option to diminish hepatitis in Im-DILI or other forms of hepatitis with a similar pathogenesis. The presentation of Im-DILI can resemble almost any form of hepatitis. This translational observation suggests to us that utilization of animal models of Im-DILI could uncover unique aspects of this disease as well as innovative therapeutic options for Im-DILI and possibly other forms of hepatitis.

1. Lee, et al., Mediators Inflamm 2010:567351
2. Liew et al., Nat Rev Immunol Feb;2010(2):103-10
3. Volarevic et al., J Hepatol 2012 Jan;56(1):26-33
4. Njoku et al., Exp Mol Pathol. 2005 Apr;78(2):87-100

Junior Faculty Award

A Novel Strategy to Treat Human Pre-Term Labor - Targeting the TMEM16/Anoctamin Chloride Channel in Human Pregnant Uterus

George Gallos, M.D.; Herng-Yu Sucie Chang, Ph.D.; Wen Fu, Ph.D.; Elizabeth Townsend, Ph.D.; Hiromi Funayama, D.D.S., Ph.D.; Charles W. Emala, M.D.
Columbia University

Introduction: Pre-term labor is a major health challenge that is associated with high maternal and fetal morbidity. Since the pharmacologic armamentarium for treating pre-term labor has limited efficacy, novel mechanisms capable of promoting uterine smooth muscle tocolysis are clinically valuable to suppress pre-term labor. We have previously described the expression of mRNA from the TMEM16/Anoctamin family of calcium activated chloride channels in murine as well as human myometrium and showed that TMEM16A antagonists suppress stretch-induced uterine contractions in a murine model. In the current group of studies, we questioned the functional implications of TMEM16A blockade on in vitro pregnant human uterine smooth muscle contractions generated by exogenous oxytocin. We also examined the ability of TMEM16A antagonists to: 1) suppress spontaneous transient inward chloride currents (STICs) (electrophysiologic phenomena associated with rhythmic contractile waves) by whole cell electrophysiology and 2) abolish oxytocin-induced elevations of intracellular calcium using real-time fluorescence imaging.

Methods: Following IRB approval, samples of pregnant human myometrium were obtained during C-section and processed for either in vitro contractile studies or were primarily dissociated to establish primary uterine smooth muscle cell cultures. To assess the functional implications of TMEM16A blockade on pregnant human uterine smooth muscle contractions, we performed organ bath experiments on excised uterine segments examining the effect of a TMEM16A inhibitor, tannic acid (200uM) on subsequent oxytocin-induced (1uM) contraction frequency and force (integrated over a period of 25 minutes). Primary human uterine smooth muscle cells were loaded with the calcium indicator Fluo-4 and the ability of tannic acid (100uM) to inhibit subsequent oxytocin-induced (1uM) calcium release was assessed with confocal microscopy. Data is presented as mean ± SEM; $p < 0.05$ was considered significant.

Results: Treatment with the TMEM16A antagonist tannic acid attenuated both the frequency (4.6± 1.3 contractions/25 min; n=5; Figure 1B) and integrated force (8446±1250 gm*sec/25 min; n=5; Figure 1C) of oxytocin-induced human uterine contractions when compared to the frequency and force measured in vehicle controls (17.4±1.4 contractions/25min; n=6; p=0.0001 and 18814±3010 gm*sec/25 min; n=4; p=0.01 respectively). Pretreatment with the TMEM16A antagonist (tannic acid 100uM) also attenuated oxytocin-(1uM) induced calcium release (5.45±2.30 ΔRFU; n=8) compared to vehicle controls (212.2±53.15 ΔRFU; n=5; p=0.01). Additionally, TMEM16A blockade reduced oxytocin-enhanced uterine smooth muscle cell pro-contractile electrophysiologic current amplitude (0.28±0.10 pA; n=4 vs 2.09±0.57 pA; n=4; p=0.020) and frequency (0.21±0.09 Hz; n=4 vs. 4.10±1.3 Hz; n=4; p= 0.025).

Conclusion: TMEM16A is expressed in human pregnant uterine smooth muscle cells. Blockade of TMEM16A attenuates oxytocin-induced contractions, abolishes oxytocin-induced calcium release and suppresses human uterine electrical STIC activity. Targeted blockade of endogenous TMEM16 receptors may represent a novel therapeutic option for patients in pre-term labor.

Prolonged Hyperglycemia Abolishes Ischemic Preconditioning in Glomerular Endothelial Cells

Katie J. Schenning, M.D., M.P.H.; Nabil J. Alkayed, M.D., Ph.D.; Michael P. Hutchens, M.D., M.A.
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Introduction: Ischemic preconditioning is a promising preventive strategy for acute kidney injury secondary to ischemia/reperfusion injury (IRI). However, there is a major barrier to the translation of this experimental strategy. Many ischemic preconditioning studies have been performed in healthy animals with no comorbidities. Clinically, the patients that experience IRI are very likely to have comorbidities such as diabetes. We set out to determine if ischemic preconditioning protects glomerular endothelial cell (GenC) monolayers from a model of IRI and whether prolonged hyperglycemia altered the effects of ischemic preconditioning.

Hypothesis: We hypothesized that ischemic preconditioning would protect GenC integrity in an in vitro model of IRI, and that this effect would be negated in the setting of prolonged hyperglycemia.

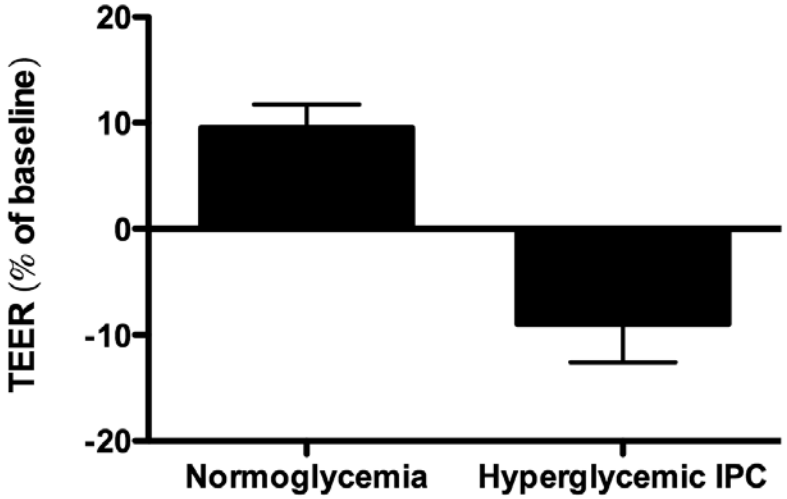
Methods: GenC were cultured on transwells in normoglycemic and normoxic conditions. After 5 days of culture, GenC were subjected to either 60 minutes of ischemic preconditioning (oxygen-glucose deprivation, OGD) or sham. GenC were returned to normoxia/normoglycemia for 18h. Both preconditioned and control groups of GenC were then exposed to an in vitro model of IRI (6 hours of OGD followed by 18 hours of reoxygenation/glucose repletion). Transendothelial electrical resistance (TEER) was used as a measure of GenC monolayer integrity, and was assessed prior to OGD and after reoxygenation/glucose repletion. Experiments were repeated on GenC cultured under hyperglycemic conditions. Statistical analysis was performed using 2-tailed Student's t-test.

Results: The normoglycemic GenC monolayers exposed to ischemic preconditioning were more resistant to OGD than unconditioned GenC as measured by higher TEER values ($p=0.02$, $n= 4$). When GenC were cultured in hyperglycemia prior to experimentation, the effect of ischemic preconditioning was lost ($p=0.08$, $n=4$). (Figure 1)

Conclusions: Our data suggests that ischemic preconditioning protects the integrity of healthy GenC monolayers in an in vitro model of IRI. However, it appears that the protective effect of ischemic preconditioning is lost in cells that are cultured in hyperglycemic conditions. In order to translate preconditioning strategies to patients, further research is needed regarding the effects of hyperglycemia and diabetes on ischemic preconditioning.

Supported by awards from the Foundation for Anesthesia Education and Research and the Collins Medical Trust.

Extra Files:
Figure 1. Prolonged hyperglycemia negated the protective effect of ischemic preconditioning in glomerular endothelial cells.



Normoglycemic GenC that underwent ischemic preconditioning had improved function compared to control GENC. Prolonged hyperglycemia negated the protective effect of ischemic preconditioning. (Mean±SEM, n=4)

Hydrogen Sulfide in High Concentrations Vasodilates the Fetoplacental Circulation in the Dual-perfused, Single Isolated Human Placental Cotyledon

Curtis L. Baysinger, M.D.; Raymond F. Johnson, B.Sc.; John W. Downing, M.D.; Jerod S. Denton, Ph.D.
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Introduction: Hydrogen sulfide (H2S), a new endogenous gasotransmitter produced in vascular endothelium from homocysteine, regulates human vascular tone1. H2S is present in the placenta and corpus cavernosum2, 3. Sodium sulfide (Na2S) in solution produces H2S and HS- to generate biphasic vascular changes in non-pregnant rodent aortas4. Lower concentrations (10 – 100 uM) constrict, higher concentrations (100 – 1600 uM) relax vasculature. H2S is intricately involved in pulmonary hypoxic vasoconstriction (PHV)5, 6. Hypoxemic fetoplacental vasoconstriction (HFPV) is analogous to PHV. We investigated the influence of H2S on the fetoplacental circulation.

Methods: With IRB approval and informed written consent fresh placentae (n = 5) were harvested at elective CS from healthy women at term. Organs were transported expediently to our laboratory where a fetal chorionic artery and vein serving a discrete cotyledon were isolated and cannulated. Three needles were inserted into the maternal placental interface. Both sides of the placenta were perfused with Krebs Ringers buffer (KRB) at constant pH (7.4) and temperature (37□C). The open (non-recirculating) model was employed. Cotyledons were perfused for an hour to stabilize pressures. Fetal perfusion rates were held constant. With constant flow, fetal arteriolar perfusion pressures (FAP) is inversely related to arteriolar vascular resistance. FAP were recorded every 5 minutes. Na2S was added to the fetal reservoir and concentrations increased incrementally every 30 minutes (10, 30, 100, 300 uM). Thereafter 5-hydroxytryptamine (5HT) was infused demonstrating normal fetoplacental vasoconstriction. FAP recorded just before every step interval was used for data analysis. One way analysis of variance compared FAPs.

Results: FAP (□ FVR) was unaffected by low Na2S concentrations (10-100 uM) but decreased significantly over time with a high concentration (300 uM) (Figure 1).

Discussion: High concentration H2S only dilated but did not constrict the fetoplacental circulation 1. Since H2S mediates PHV, experiments utilizing H2S generators and inhibitors are needed to determine how H2S affects human HFPV in vitro.
*AUA member.

References:

1. Liu et al J Cardiovasc Pharmacol 2011;58:560.
2. Holwerda et al Placenta 2012; 33:518.
3. Di Villa Bianca et al PNAS 2009;106:4513.
4. Lim et al Am J Physiol Cell Physiol 2008;295:C1261.
5. Skovgaard et al Am J Physiol 2012;303:R487.
6. Olson et al Am J Physiol Regul Integr Comp Physiol 2010;298:R51-60.

Methylnaltrexone Inhibits Opioid- and Growth Factor-Induced Human Lung Cancer Proliferation, Migration and Epithelial Mesenchymal Transition (EMT)

Jonathan Moss, M.D., Ph.D.; Frances E. Lennon, Ph.D.; Tamara Mirzapoiazova, M.D., Ph.D.; Bolot Mambetsariev, Ph.D.; Ravi Salgia, M.D., Ph.D.; Patrick A. Singleton, Ph.D.
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Background: Recent epidemiologic studies suggesting differences in cancer recurrence contingent on anesthetic regimens have raised the possibility that the mu opioid receptor (MOR) can influence cancer progression. Based on our previous observations that overexpression of MOR in human non-small cell lung cancer (NSCLC) cells increased tumor growth and metastasis, this study examined whether MOR antagonism regulates growth factor receptor signaling and epithelial mesenchymal transition in human NSCLC cells.

Methods: We utilized specific siRNA, shRNA, chemical inhibitors, overexpression vectors and the peripheral MOR antagonist, methylnaltrexone (MNTX), in human H358 NSCLC cells that were either untreated or treated with various concentrations of DAMGO, morphine, fentanyl, EGF or IGF. Cell function assays (proliferation, migration), immunoblot and immunoprecipitation assays were then performed.

Results: Our results indicate MOR regulates opioid- and growth factor-induced EGF receptor signaling (Gab-1, Akt and STAT3 activation) which is crucial for consequent human NSCLC cell proliferation and migration. In addition, human NSCLC cells treated with opioids, growth factors or MOR overexpression exhibited a concentration-dependent increase in snail, slug and vimentin and decrease ZO-1 and claudin-1 protein levels, results consistent with an EMT phenotype. Further, these effects were reversed with MNTX at clinically relevant concentrations, silencing (shRNA) of MOR and Gab-1 expression and chemical inhibition of Akt and STAT3.

Conclusions: Our data suggests a possible direct effect of MOR on opioid- and growth factor-signaling and consequent proliferation, migration and EMT transition during lung cancer progression. Such an effect provides a plausible explanation for the epidemiologic findings. Our observations further suggest that examination of MOR antagonists including MNTX in NSCLC merits further study as a therapeutic option.

OP-CS 67 (56)

Preservation of B Cells in Intra-abdominal Sepsis Decreases Mortality

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Introduction: Sepsis and the Systemic Inflammatory Response Syndrome (SIRS) are the primary cause of death in Intensive Care Units across the globe. The mechanism underlying the pathophysiology of the initial systemic hyper-inflammatory response and subsequent immune suppression remain incompletely delineated. The septic state is characterized by a profound depletion of B-lymphocytes. The absence of these cells may be required for progression to sepsis-induced mortality.

Hypothesis: The B-cell survival factor, BLyS, can protect B-cells from depletion in septic mice and prevent mortality.

Methods: Male Balb/c mice were divided into 2 groups. Group A (n=18) received daily intra-peritoneal injections of recombinant B-Lymphocyte Stimulator (BLyS) protein (10mcg) for 7 days. Group B mice (n=18) were injected with saline as a control. Both groups were then subjected to cecal ligation and double puncture (CLP) using a 23G needle. Mice were sacrificed at serial time points (12, 24, 48 and 72 hours after CLP) and the peripheral blood and lymphoid tissue (spleen, lymph node, bone marrow) were harvested and analyzed via flow cytometry.

Results: CLP reduced total B-cell counts in saline-treated controls from 35.3 x 106 at t=0 to 6.94 x 106 t=48 hours after CLP. Follicular and transitional B cell subsets were reduced, but the most profound effect involved the marginal zone, where B cell counts were reduced 10-fold, from 14.9 x 106 to 1.48 x 106. In contrast, administration of BLyS preserved total B cell counts; 48 hours after CLP the number of B-cells (25.6 x 106) in group A mice was not reduced.(fig.1) In addition, BLyS treatment conferred a survival benefit. 12/18 group A mice were alive 2 weeks after CLP while none of the saline-treated controls survived for more than 72 hours.(fig. 2) Serum BLyS levels were initially elevated at t=0 in the animals treated with BLyS, but at t=24 and t=48 hours post CLP the levels were similar to those of saline treated controls.

Conclusions: Exogenously administered BLyS protects the B-cell compartment of mice subjected to CLP from depletion. The maintenance of a mature B-cell compartment in these septic mice is associated with a significant survival advantage. The potential therapeutic utility of recombinant BLyS for the treatment of sepsis warrants further investigation.

Endogenous Ubiquinol, Oxidative Stress, and Kidney Injury Following Cardiac Surgery

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Intraoperative oxidative stress independently predicts the development of acute kidney injury (AKI) following cardiac surgery, and the pattern of F2-isoprostane vs. isofuran expression in the plasma and urine might be consistent with renal mitochondrial dysfunction. We measured ubiquinol, ubiquinone, F2-isoprostane, and isofuran concentrations prior to, during, and one day following cardiac surgery in 40 patients that developed stage I AKI (defined using AKIN criteria) and 40 risk-matched control patients to test the hypothesis that endogenous ubiquinol and ubiquinol/ubiquinone redox ratios are associated with oxidative stress and kidney injury following cardiac surgery.

Baseline estimated glomerular filtration (56.7 ± 22.8 ml/min/1.73 m2 vs. 55.2 ± 18.6), BMI (31.0 ± 6.6 kg/m2 vs. 30.2 ± 5.7), and duration of cardiopulmonary bypass (167 ± 71 minutes vs. 162 ± 60) were similar between AKI and control subjects. Age, gender, preoperative statin use, use of cardiopulmonary bypass, intraoperative transfusions, and perioperative exposure to iodinated radio contrast were also similar between groups. Preoperative concentrations of ubiquinol and ubiquinone were 590 ng/ml (IQ range 346, 870) and 87 ng/ml (53, 137) in AKI subjects vs. 388 (284, 587) and 60 (38, 103) in control subjects (P=0.02 ubiquinol and P=0.02 ubiquinone). Ubiquinol concentrations decreased 234 ± 262 ng/ml during surgery in all subjects but 164 ng/ml more (95% CI: 50 to 279, P=0.003) and 11.7% more (P=0.05) in those subjects that developed AKI (Figure). Ubiquinol/ubiquinone redox ratios did not change significantly during surgery and were not different between AKI and control subjects but were highly associated with plasma expression of F2-isoprostanes and isofurans. Each 10 unit increase in baseline redox ratio, indicative of reduction potential, was associated with 12.2 pg/ml (95% CI: 5.3 to 19.2, P=0.001) and 14.7 pg/ml (95% CI: 3.2 to 26.2, P=0.01) reduction in circulating F2-isoprostanes and isofurans on postoperative day 1, adjusted for BMI and statin use. In addition, increased baseline ubiquinol concentrations were associated with decreased plasma F2-isoprostane concentrations at baseline (Spearman correlation r=-0.26, P=0.02), during surgery (r=-0.34, P=0.002), and on postoperative day 1 (r=-0.36, P=0.001). Plasma concentrations of isofurans were 11.5 pg/ml higher in AKI subjects compared to control subjects during the perioperative period (95% CI 0.5 to 22.4, P=0.04). Urine concentrations of F2-isoprostanes and isofurans were similar between groups although isofuran/F2¬-isoprostane ratios were 113% higher on postoperative day 1 in AKI subjects (P=0.002, Figure). Postoperative day 1 isofuran/F2-isoprostane ratios were also increased in patients with low baseline ubiquinol/ubiquinone redox ratios (r = -0.26, P=0.02, Figure) and may indicate oxidative stress in presence of dysfunctional mitochondria and AKI.

Ubiquinol plasma concentrations decrease more during cardiac surgery in patients that develop AKI compared to risk-matched controls, and high baseline ubiquinol/ubiquinone redox ratios are associated with reduced oxidative stress during and following surgery.

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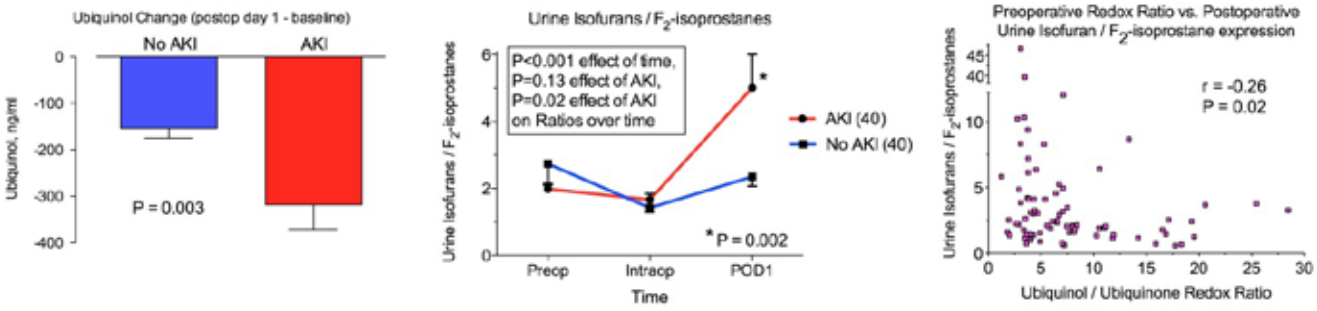

Interplay Between Toll-Like Receptors and Complement Factor B In Polymicrobial Sepsis

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Introduction: Toll-like receptors (TLRs) and the complement system are essential parts of innate immunity. Complement factor B (cfB) is a necessary component of the alternative pathways (AP). Crosstalk exists between the two systems. But, how the two components interplay and their role in the pathogenesis of sepsis is poorly understood.

Methods: Macrophages (M)and cardiomyocytes (CMs) were stimulated with TLR ligands. Polymicrobial sepsis was created by cecum ligation and puncture (CLP). Complement mRNA and protein were determined by qRT-PCR, Western blot, and immunohistochemistry (IHC). Cytokines were determined using multiplex assay. Cardiac function was assessed in a Langendorff perfusion system. Acute kidney injury (AKI) was assessed by kidney NGAL and KIM-1 expression. ROS was measured with redox sensitive DCF dyes.

Results: Both TLR2 and TLR4 stimulation markedly increased cfB mRNA and protein expression in M. In CMs, TLR2 and TLR4 stimulation induced a robust cfB (217±54 and 578±54 fold, respectively, n=4-5, P<0.01) and a modest C3 mRNA expression, but not C4 or C5. In vivo, CLP induced a time-dependent increase in cfB expression in all major organs (Fig. 1a), and the increase in the heart is in part MyD88-dependent (Fig. 1b, 1c). CLP also led to a systemic AP activation. IHC indicated that sepsis-induced cfB expression was mainly located in CMs as well as kidney tubular epithelial cells (Fig. 1d). Importantly, septic cfB-/- mice had improved survival compared with septic WT mice (58% vs. 35% on day 14) (Fig. 1e), preserved cardiac function as demonstrated by significant increased LVDP (69±6 vs. 53±2 mmHg), dP/dt max (3017±297 vs. 2440±101 mmHg/s), dP/dt min (1867±200 vs. 1324±74 mmHg/s) (Fig. 1f) and attenuated AKI as evidenced by reduced kidney NGAL (139±36 vs. 23±3 fold) and KIM-1 (20±9 vs. 2±0.3 fold) mRNA (Fig. 1g). This protective effect was associated with decreased bacterial loading, systemic/local cytokine production, reduced peritoneal cells ROS in septic cfB-/- mice. Attenuated C3dg fragments in serum and lavage as well as decreased C3 fragment deposition in the kidney of cfB-/- mice may contribute to organ protection during sepsis.

Conclusion: Our studies demonstrate that TLR2/4 activation in M and CMs in vitro and polymicrobial sepsis in vivo stimulate cfB expression in the blood and multiple organs. cfB may play a role in mediating cardiac dysfunction, AKI, systemic inflammation, ROS production, and contribute to mortality during polymicrobial sepsis.

Figure 1: a, cfB immunoblotting of different organs. Ponceau stain was used as loading control; b, cfB qRT-PCR. cfB mRNA was measured in the hearts of WT and TLR-/- mice 24 h post-surgeries. (** P<0.01, # P<0.001 vs. sham, * P<0.05 vs. WT-CLP, n= 3-10); c, cfB protein expression in the heart; d, cfB IHC of the heart and kidney; e, Survival following CLP (* P<0.05); f, Cardiac function tested 24 h post-surgeries (*P<0.05, **P<0.01, #P<0.001, n=3-10); g,Kidney NGAL and KIM-1 mRNA (*P<0.05,**P<0.01, n=4-7)

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MicroRNAs and Anesthetic Cardioprotection in Diabetes

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Introduction: MicroRNAs are endogenous small RNA molecules that regulate a wide range of cellular functions primarily through reduction of target proteins. Several microRNAs have been shown to play important roles in cardiac injury,(1,2) and also contribute to the development of diabetic complications (3,4) and cardiac preconditioning.(5-7) We explored the contribution of microRNAs, since their role in anesthetic cardioprotection remains largely unknown. We utilized a model of the patient-specific induced pluripotent stem cells (iPSCs) differentiated into the cardiac lineage in order to delineate the environmental and cellular mechanisms responsible for overturning anesthetic cardioprotection in diabetes. We hypothesized that miR-21 contributes to cardioprotection conferred by anesthetics in human cardiomyocytes and that diabetic conditions compromise this protection in part via suppression of miR-21.

Methods: We have developed and validated a clinically relevant model of cardioprotection using human cardiomyocytes differentiated from the iPSCs derived from non-diabetic individuals (N-CM) and patients with type 2 diabetes mellitus (T2-CM).(8,9) The advantage of this approach is that the effect of anesthetics can be evaluated in human cardiomyocytes, thereby, capturing the complex physiologic interactions at the patient-specific myocyte level.

Results: Our results indicate that cardiomyocytes derived from type 2 diabetes-specific stem cells recapitulate the phenotypic findings from type 2 diabetic patients. For instance, T2-CM exhibited a suppression of protein kinase B (Akt) and activation of glycogen synthase kinase-3 (GSK-3), compared to N-CM; indicating that this pathway is compromised in cardiomyocytes derived from diabetic individuals (Fig.1). Similar findings were reported in the diabetic individuals.(10) In addition, we examined whether isoflurane could delay oxidative stress-induced mitochondrial permeability transition pore (mPTP) opening in T2-CM and found that the effects of isoflurane were significantly attenuated as compared to N-CM (Fig.2). Finally, isoflurane increased miR-21 abundance in N-CM, but not in T2-CM (Fig.3). The increase of miR-21 abundance was completely lost even in N-CM pre-treated with high ambient glucose.

Summary: Diabetes and hyperglycemia substantially increase perioperative cardiovascular risk, with few mitigating strategies. Our data indicate an important role of miR-21 in isoflurane-induced cardioprotection and its impairment by diabetic conditions that may suggest new therapeutic targets for reducing perioperative cardiovascular morbidity and mortality in high-risk patients.

References: 1)Nature.2011;469(7330):336-42; 2)Circ Res.2009;104(6):724-32; 3)Diabetes.2011;60(7):1825-31; 4) Diabetes.2011;60(7):1832-7; 5) J Biol Chem.2009;284:29514-25; 6) Cardiovasc Res.2010;87(3):431-9; 7)Circ Res.2009;104(5):572-5; 8) Anesthesiology.2010;113:906-16; 9)Anesthesiology.2012;117:735-44; 10)J Cell Moll Med.2010;14:1740-6.

Critical Role of Interleukin-11 in Isoflurane-Mediated Protection Against Ischemic Acute Kidney Injury

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Introduction: Acute kidney injury (AKI) is a major clinical problem without effective therapy (1). We demonstrated previously that isoflurane protects against renal ischemia-reperfusion (IR) injury by attenuating necrosis, apoptosis and inflammation (2). However, the isoflurane therapy for critically ill patients may be limited by its anesthetic and cardiovascular effects. One way to mitigate this is to utilize the distal signaling molecules synthesized with isoflurane treatment. Interleukin-11 (IL-11) is a clinically used hematopoietic cytokine that increases platelet count upon long term use (3). Recent studies suggest that IL-11 also attenuates necrosis, apoptosis and inflammation after intestinal, cardiac and renal IR injury (4). Here, we tested the hypothesis that isoflurane protects against ischemic AKI by direct induction of kidney IL-11 synthesis.

Methods: To test whether isoflurane induces renal proximal tubule IL-11 synthesis, human proximal tubule (HK-2) cells were treated with 1.25-2.5% isoflurane or carrier gas (room air+5% CO2) for 3-16 hr. We also anesthetized mice with 1% isoflurane or with equi-anesthetic dose of pentobarbital for 4 hr. To test the role of IL-11 in isoflurane-mediated renal protection, we subjected IL-11 receptor (IL-11R) wild type (WT) or deficient (KO) mice to 30 min renal ischemia followed by reperfusion under 4 hr of pentobarbital or isoflurane (1%) anesthesia. We also pretreated IL-11R WT mice with IL-11 neutralizing antibody or control isotype antibody (1 mg/kg i.p.) 30 min. before isoflurane anesthesia. Finally, we tested whether exogenous administration of recombinant human IL-11 (1 mg/kg s.c.) immediately before or 30 min after reperfusion mimics isoflurane-mediated protection against ischemic AKI.

Results: Isoflurane increased IL-11 mRNA (Fig. 1A) and protein in HK-2 cells (Fig. 1B). A specific inhibitor of ERK MAPK (PD98059) attenuated isoflurane-mediated induction of IL-11 in HK-2 cells (Fig. 1B). Mice anesthetized with isoflurane showed significantly increased kidney IL-11 mRNA (Fig. 1C) and protein expression (Fig. 1D) compared to pentobarbital anesthetized mice. Furthermore, IL-11R WT mice subjected to renal IR under pentobarbital anesthesia developed severe AKI with large increases in plasma Cr 24 hr after injury (Fig. 2). In contrast, IL-11R WT mice anesthetized with 1% isoflurane after renal ischemia had significantly reduced renal IR injury. Supporting a critical role of IL-11 in isoflurane-mediated renal protection, isoflurane failed to protect IL-11R KO mice against ischemic AKI. In addition, IL-11 neutralizing antibody abolished the renal protection provided by isoflurane in IL-11R WT mice. Finally, IL-11R WT mice treated with human recombinant IL-11 immediately before or 30 min after reperfusion were significantly protected against renal IR injury.

Conclusions: Taken together, our studies suggest that isoflurane induces renal tubular IL-11 to protect against ischemic AKI. Exogenous administration of IL-11 may have reduce the morbidity and mortality arising from AKI without the systemic effects of volatile anesthetics.

References

1. Contrib Nephrol 165: 1, 2010.
2. AJP Renal Physiol 293: F713, 2007.
3. Oncology (Williston Park) 14: 41, 2000.
4. AJP Renal Physiol 303: F1216, 2012.

Resident Travel Award

Novel Chloride Channel Blockers Relax Airway Smooth Muscle: Potential New Tools to Treat Bronchospasm

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Introduction: Perioperative bronchospasm refractory to β-agonists continues to challenge anesthesiologists and intensivists. We questioned whether chloride channels/transporters are novel targets in the treatment and prevention of bronchospasm. Calcium activated chloride channels (CaCCs) and the sodium potassium chloride cotransporter (NKCC) are 2 potential targets on airway smooth muscle that control cellular chloride flux. In previous studies, combined blockade of CaCCs and NKCC with non-selective CaCC antagonists relaxed acetylcholine induced contractions. We have screened a library of novel compounds, derivatives of anthranilic and indanyloxyacetic acid, that were previously developed as chloride channel antagonists in the kidney. We hypothesized that members of this library would be more potent and/or specific than known CaCC blockers, and that further analysis of the structural and mechanistic differences could aid in novel bronchodilator drug development.

Methods and Results: All studies received IACUC or IRB approval. Closed guinea pig tracheal rings were suspended at 1g tension in oxygenated buffer at 37°C. The library was initially screened by the compounds' ability to relax contractions induced by potassium channel blockade with tetraethylammonium chloride (TEA). 4 of the 20 compounds screened were found to relax a TEA induced contraction. Compounds 1 and 13 were further studied for their potential to relax the maintenance phase of contractions induced by the natural endogenous bronchoconstrictor, acetylcholine (Ach). Treatment with 100uM compound 1 or 13 alone each significantly relaxed contraction (42.9 +/- 4.24% and 65.12 +/- 4.96% of initial Ach muscle force, respectively), while in combination with the NKCC inhibitor, bumetanide (10uM) they relaxed an Ach contraction to an even greater extent (26.54% +/- 2.94% and 28.99% +/- 6.66% of initial Ach muscle force, respectively). Additionally, pretreatment with either compound in combination with bumetanide prior to an acetylcholine challenge attenuated a subsequent contraction.

Human airway smooth muscle from lung transplants were suspended and contracted with Ach. Treatment with 100uM of compounds 1 or 13 relaxed an Ach induced contraction (23.7 +/- 7.8% and 37.4 +/- 5.9% of initial Ach muscle force, respectively). For cellular assays, human airway smooth muscle cells were cultured. Compounds 1 and 13 hyperpolarized the plasma cell membrane (which favors relaxation) as measured by the FLIPR potentiometric fluorescent indicator (143% and 55% decrease in fluorescence compared to vehicle, respectively, n=5). In whole cell patch clamp recordings, compound 13 blocked spontaneous transient inward chloride currents (n=2).

Conclusions: We have identified two novel chloride channel blockers which relax either an established TEA or Ach contraction. Additionally pretreatment attenuated an Ach contraction, and caused a hyperpolarization of plasma membrane potential and an inhibition of chloride current in human airway smooth muscle cells. These functional and electrophysiologic data suggest that modulating airway smooth muscle chloride flux is a novel therapeutic target in asthma and other bronchoconstrictive diseases.

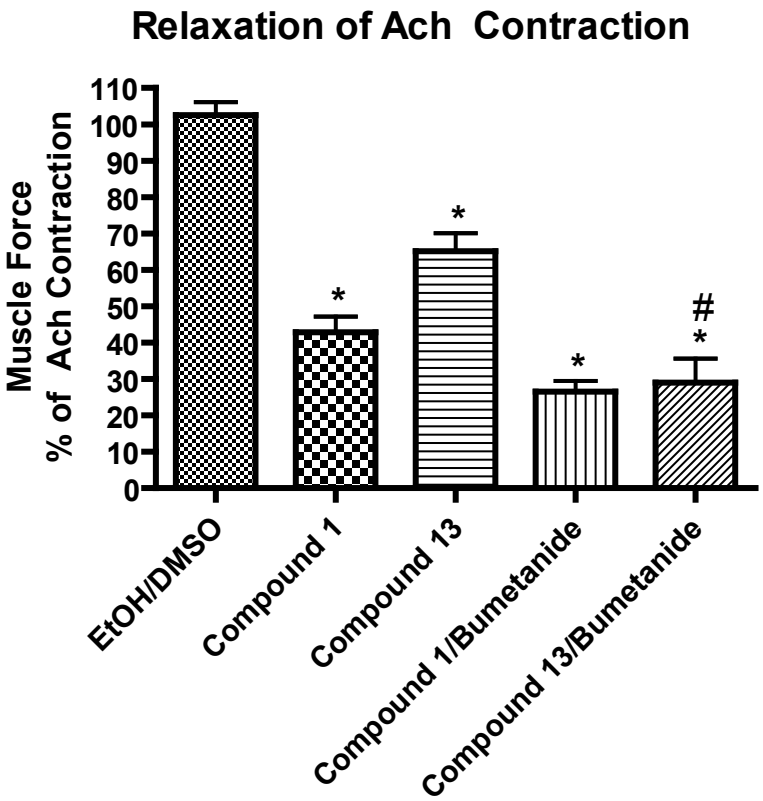

Figure 1. Chloride channel/transporter blockade of an established achetylcholine (Ach) concentration in guinea pig airway smooth muscle. The relaxation induced by the novel chloride channel blockers (100uM compound 1 and 13) was further potentiated by co-blockade of the NKCC by 10uM bumetanide. * $p<0.01$ compound to respective vehicle control # $p<0.01$ compound 13 to compound 13/bumetanide, n=5

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